Food and Drug Administration
Center for Food Safety and Applied Nutrition

Meeting of

Food Advisory Committee (FAC)

September 29, 2014

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TABLE OF CONTENTS

P R O C E E D I N G S (8:30 a.m.)

Agenda Item: Call to Order and Introduction of Committee

DR. HAYES: Good morning. My name is Wally Hayes. I am the acting chair for today and tomorrow's gathering. According to our agenda, I am calling the meeting to order, and we will have introductions. We will just go around the table and introduce ourselves.

DR. LINKOV: Igor Linkov. I am with Army Engineer Research and Development Center.

DR. MEYER: Sharon Meyer, University of Louisiana at Monroe.

DR. WILLETT: Walter Willett, Departments of Epidemiology and Nutrition at Harvard School of Public Health.

DR. RUZANTE: Juliana Ruzante with the Pew Charitable Trusts.

DR. WALLACE: Ken Wallace, University of Minnesota Medical School.

DR. MCBURNEY: Michael McBurney, DSM Nutritional Products.

DR. ROSS: Catherine Ross, Penn State University, Nutritional Sciences.

DR. SHREFFLER: Wayne Shreffler, Pediatric Allergy and Immunology at Mass General, Harvard Medical

School.

DR. SANTERRE: Charlie Santerre, food toxicologist at Purdue University.

DR. SWAIN: James Swain, Case Western Reserve University, Department of Nutrition, School of Medicine.

DR. RANGAN: Uryashi Rangan, with laryngitis, from Consumer Reports.

DR. ARMBRUST: Kevin Armbrust, Louisiana State University.

DR. BERU: Good morning. My name is Nega Beru. I am the Director of Office of Food Safety in CFSAN.

MR. LANDA: Good morning. I am Mike Landa. I am Director of CFSAN. Hello.

DR. HAYES: Thank you very much. I think now we will have Karen Strambler. She is going to go through the conflict of interest statement and any other housekeeping items that she has.

Agenda Item: Conflict of Interest Statement

MS. STRAMBLER: Good morning. The Food and Drug Administration is convening today's meeting of the Food Advisory Committee under the Federal Advisory Committee Act of 1972. With the exception of industry representatives, all members of the committee are subject to federal conflict of interest laws and regulations.

The following information on the state of the

committee's compliance with the federal ethics and conflict of interest laws covered by, but not limited to, those found in 18 USC, Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that the members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC, Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest

Related to the discussion of today's meeting, members have been screened for potential financial conflicts of interest of their own, as well as those imputed to them of their spouses, minor children, and, for the purpose of 18 USC, Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, cooperative research and development agreements, teaching, speaking, writing, patent royalties, and primary employment. Based on the agenda of today's meeting and the financial interests reported by committee members, no conflict of interest waivers have been issued.

We want to remind the members that this meeting is a particular matter of general applicability, and the discussion should not involve any specific products or firms.

Dr. Harry Fong, Dr. Donald Orth, and Dr. Richard Durst are members of the committee who were unable to attend due to personal reasons.

I would like to remind everyone that the members of the public and the press are not permitted in the committee area.

Your FDA communication officer for today is Noah Bartolucci, but I don't see him here right now. I request that reporters wait to speak to Noah until the committee meeting has been concluded.

Also, I just want to remind everyone to please turn your mobile phones on silent.

The next voice you will hear is Mike Landa, who is our director of the Center for Food Safety and Applied Nutrition.

Agenda Item: Opening Remarks

MR. LANDA: Thanks, Karen.

I don't have any slides. That's the good news. I will be fairly brief before turning this over to the people who are, for us, going to make the expert presentations.

First, let me thank you for your participation. We all know you're busy folks, so we very much appreciate your taking time from your busy schedules to help us out.

Let me also say that as a reward for helping us out, we are trying to do more committee meetings every year, so we're actually going to do a second later this year which I'll tell you about in a minute. We are already planning for two next year, and who knows, maybe we'll get to a third. In any case, the point is we're planning on making more use of you in the future, which I think will be good for us, and I hope it will be good for you.

With that, I will talk just a little bit about the charge. Nega Beru is going to go into it in great detail.

Risk-ranking and risk-prioritization methods are increasingly being developed and utilized by federal regulatory agencies to assist with resource allocation. The need for risk ranking or risk prioritization is inherent to decision making, given the multitude of potential food safety hazards and the need to focus limited resources by targeting regulatory programs on the greatest risks among the greatest hazards, commodities, and stages in the food supply chain.

I would also say that even if our budgets were very, very, very substantially larger, we would still want

to engage in this type of exercise. You still need to figure out what's the most important thing to do. If your risk ranking is 1 to 100, maybe your dollars will let you get 1 to 10 instead of 1 to 90, but I think you still want to engage in the process we've asked you to help us with.

FDA and FSIS have been developing risk tools and regulatory programs to improve surveillance and subsequent management of chemical contaminants in the food supply. In developing and evaluating the effectiveness of these programs, agencies must consider a number of factors. A key factor is the purpose of the program; that is, how will the data collection or the results of the risk ranking/risk prioritization be used to support regulatory decisions? We are a regulatory agency, although there is a scientific component to it, a foundational component. It's not scientific inquiry for the sake of scientific inquiry. The inquiry has got to relate to our regulatory programs.

Although the purposes of different programs and the types of tools developed will vary, it may be possible to identify fundamental elements that are applicable across programs and that consider basic areas useful or necessary to be addressed in designing or evaluating a data collection/risk-ranking/prioritization program. At this meeting we will be asking you to provide input on the development of the characteristics for data collections and

risk-ranking/risk-prioritization models. These characteristics would be useful in framing the fundamental elements needed to design or evaluate the two agencies' food and veterinary programs.

Erik Mettler in a few minutes will talk about risk-informed decision-making process generally, and then Dr. Nega Beru will take you through the charge. But first I want to update you on a couple of related activities.

First, something we have been undertaking for the last 18 to 24 months known internally as the Chem Safety Review. We, meaning CFSAN, CVM, and the Office of Foods and Vet Medicine, have been conducting a review of the chemical safety assessment program across the two centers. The review had a number of elements:

Anonymous and confidential interviews of CFSAN and CVM scientists who volunteered to participate. We got about an 80 or 85 percent participation rate. A contractor did the interviews based on questions we developed, wrote up the results, but they were anonymized. We don't know who said what to the contractor, at least not on an individual basis.

There were then listening sessions with representatives of consumer groups and the food industry and with CFSAN epidemiologists. Again, no names were taken.

We also had interviews of CFSAN alumni and of officials from other federal agencies with similar programs, principally, as one would expect, EPA.

Then we had four independent outside consultants look at all this material after meeting with us and try to make sense of it and to make recommendations to us. These consultants are experts in, as I recall, epidemiology, risk assessment, and public health more generally.

Last month, after we pulled together all the information, we posted it on the Web. If you're interested it is on fda.gov under the heading "OFVM Chemical Safety Assessment Review." It is fairly dry and there's a lot of it, but I think, for those of you who have the time and interest, it is worth looking at.

As a result of this review, we are undertaking several initiatives. One is to update what is called the Redbook, which is our tox guidance for food ingredients. It hasn't been updated in a number of years. We're planning on doing that with a lot of public process I think initially. I am hoping later this year we'll have a meeting of some sort at which we unveil what amounts to an extraordinary, exquisitely detailed table of contents, so people can get a sense of what we think should be in and, by virtue of its absence, what should not be in the Redbook.

We are also going to update our Risk Analysis Framework, which dates from 2002. We think it's time to do that. We're going to also develop some SOPs for conducting chemical safety and risk assessments within CFSAN and CVM across the programs, so we will get a kind of consistency that we may not yet have achieved.

Finally, we are launching a pilot. You may recall our discussion last year about detecting signals or problems with chemicals in foods, cosmetics, dietary supplements. The wheels of action grind exceedingly slowly in the government, but grind they do. We will be launching this pilot this fall. We have lined up a contractor. The contractor is going to have to do a lot of the heavy lifting.

We are going to have a couple of FTEs assigned to this full time, and then we will have individuals from various program offices on a team to work with us on this. Again, we expect to start that in the fall. It will be run out of our Office of Analytics and Outreach, which has a great deal of expertise already in databases, bioinformatics, and statistical and scientific projects.

Finally, and partly an outgrowth of the Chemical Safety Review — and this is the next advisory committee meeting we'll be doing in December — on susceptible populations and the need to look at scientific

considerations surrounding potentially susceptible populations and life stages and the circumstances under which CFSAN would decide to conduct a separate safety or risk assessment to take into account such populations or life stages. It has arisen recently in the context of inorganic arsenic, where the NRC suggested that a separate risk assessment should be conducted for certain vulnerable populations rather than relying on the assessment for the general population as a whole.

People, of course, differ in susceptibility from the effects of particular chemical exposures because of factors such as genetics, gender, socioeconomic and geographic status, predisposition to diseases, and other conditions. These factors are broadly considered to include any factor that increases or decreases the response of an individual to a dose relative to a typical individual in the population.

We are planning now on holding that meeting on December 16-17 to discuss issues again around susceptible populations and life stages and look forward to having that conversation with you as we look forward to today's meeting.

With that, let me turn it over to Erik Mettler, who will be followed by Nega Beru.

Agenda Item: Risk-Informed Decision-Making Process

MR. METTLER: Thank you. I just want to frame everything up for this discussion today and also, as Mike said, say that in the future we're going to be using you guys quite a bit more.

As we discussed, we're going through a variety of different types of risk things today. One thing I want to talk to you about is the general risk-informed decision-making process as a whole. Obviously, it is one piece of it.

Most of you are familiar with the Enhancing Food Safety report, IOM, 2010. This is the general definition for risk-informed decision making that we are working with right now.

To boil this down — everyone can read the slide — but basically where do we get the biggest bang for the buck with the limited resources we have. A very simple idea. I think everyone in here understands it. Everyone here applies it in their own specific way.

Also in the IOM report, there was a framework for implementing the steps for a risk-informed system. Again, it's pretty straightforward: strategic planning, where are we going, applying a set of public health risk rankings, coming up with a ranking of what we should be focused on,

using the targeted information to really hone in down, go through analysis of that, develop an intervention plan, and then really review and monitor it — again, very simple, what's the life cycle of this and how to actually move forward with this.

One thing that we really are trying to do is move away from the yearly, annual, day-by-day reactive sort of thing and move to a progressive, long-term public health strategic plan and try to measure things against that.

This being said, this is really nothing new for CFSAN. CFSAN has been doing it for quite some time now. This is a process they've had in place for a pretty long time. So the question really is, since they've been doing this for a while, why are we addressing it now?

Well, times have changed. There is more information. There's a new generation, new risk tools, new risk rankings that you're going to hear about today. The systems, both internally and externally, and how we are actually using our partners both from state, local, private industry and elsewhere, are really addressing — we are actually trying to figure out how we can add different types of criteria into this model.

Then I think one of the largest pieces is the transparency and communication and evaluation pieces of this. How do we communicate this? How do we work with all

the stakeholders both internally and externally, federal government, to make sure that we can get the biggest bang for the buck?

Relatively speaking, again, everyone is seeing the hazards out there. You can actually do a variety of different things by applying public health criteria to it. It comes up with a very nice, neat model – the highest risk on top and as it cascades down.

The complexity really comes in when you start adding the non-public health criteria. You have congressional mandates, at least from our side, or state mandates; stakeholder concerns, both internal and external, every which direction; costs – how much does it actually cost to address specific things, and how much money do we actually have and resources to put against these specific hazards? And the feasibility of each mitigation to go into these things.

It might actually turn out something different, that it might look like this. I'm sure you guys have seen this before. This is something that we cannot do alone, and we are going to have to look to you guys quite a bit to help us and really progress this to the next level; be transparent about how we can have this, because, obviously, if we come up with a risk ranking that is completely different than what the actual risk is, from a

prioritization standpoint, there are going to be a lot of questions. A lot of questions could be a lot of problems for a lot of people, and we want to make sure that we get this right in the future.

Obviously, today the focus of the meeting is going to be putting it back to the IOM framework. This is the easiest one to map to. We go over the high-risk foods and the most significant contaminants lists, data collection, sampling, and surveillance programs, really hitting all these individual pieces.

But the main point for all of you guys that I really want to stress as you go through this meeting is that we are going to come back to you and really talk about the entire process and focus on the strategic planning step and step 3 and step 6 as well, to bring all of this together so that at the end of the day we can talk about the entire process and that it goes the complete circle, and be transparent along the entire thing.

With that, I will turn it over to Nega and he will go through the specifics.

DR. HAYES: Before we turn it over, Erik, if you don't mind, if there are any questions by any members of the committee, I am sure you won't mind answering them now.

MR. METTLER: Absolutely.

DR. HAYES: Are there any questions that anybody

might have for this particular speaker?

(No response)

It looks like you're walking away unscathed.

MR. METTLER: This time. This time, I'm sure. Thank you.

DR. HAYES: Thank you.

Agenda Item: Overview of Charge and Questions

DR. BERU: Good morning again. My role is to tell you what the charge is and the questions we've developed to frame the discussion.

The charge to the committee is: "The Federal Advisory Committee is requested to provide FDA input into the development of the characteristics for data collection and risk ranking/prioritization models."

As Mike said, "The characteristics would be useful in framing the fundamental elements needed to design or evaluate these programs."

The questions we've developed to frame the discussion are: "What factors, considerations or criteria need to be considered when selecting which food/contaminant pair to sample and test?"

"In the development of models to identify and rank priorities, what factors/criteria need to be considered when 'aggregating' or binning foods? Chemical contaminants?"

"When using a risk scoring process, what factors/criteria should be considered in deciding where to draw the line – higher versus lower risk?"

"What factors should be considered when establishing the frequency and duration of testing certain chemical compounds?"

"What factors should be considered in deciding to continue testing versus end testing?"

And finally, "What factors should be considered where (geographic location or farm-to-fork food supply continuum) samples should be taken for testing?"

These are the questions. Again, to help frame the discussion, we will be providing you with a number of presentations on what current compliance programs will we test for chemicals. Dr. Paul South will present FDA's current compliance programs; namely, pesticides and industrial chemicals in domestic and imported foods. This has two components to it, a pesticides component as well as a dioxin component.

Then we have the toxic elements in imported and domestic food and foodware compliance program, where we test for toxic elements in foods and foodware. But this program also includes testing for radionuclides in food.

Then we have mycotoxins in domestic and imported foods compliance programs where we test for a number of

mycotoxins, including aflatoxin, fumonisins, deoxyvalenol, botulin in apple juice, and ochratoxin A.

Lastly, we have a chemotherapeutics in seafood compliance program, where we test for drugs such as chloramphenicol, natural furans, and the quinolols, to name just a few.

Dr. Paul South also worked with the FDA's Total Diet Study, which is an ongoing program, a surveillance program for various contaminants and nutrients in foods. There are really hundreds of pesticides, toxic elements, and nutrients. From time to time we actually use this program when we need data on a given contaminant, as we did, for example, for perchlorate in foods or acrylomide in foods, dioxins and PCBs in foods.

Dr. Patty Bennett will be presenting FSIS's National Residue Program. The current focus of this program is on veterinary drugs and pesticides in meat, poultry, and egg products — whether there is a plan to expand the program to other chemical hazards.

We will also present a number of models that have been developed, one in connection with the Food Safety Modernization Act, Section 104, Performance Standards. This is to develop a list of the most significant foodborne contaminants.

Another model which will be presented by

Dr. Yuchuan Chen, the High Risk Foods Model. This is in connection with FSMA Section 204, which directs us to identify high-risk foods for increased recordkeeping requirements, for example.

Then Dr. David LaBarre will be presenting FSIS's model to run the chemicals and group in "bins."

I forgot to list on my slides one other presentation, which is by Dr. Heather Tate of CVM. She will be presenting The Role of NARMS in Risk Analysis.

With that, I would like to invite Dr. South to come and walk you through the compliance programs and the TDS.

DR. HAYES: Before you depart the podium, again, are there any questions or comments for our speaker?

(No response)

You might want to look in your folder. The first document in the folder will be the charge and questions that we'll be talking about later on.

Thank you very much.

Agenda Item: Compliance Programs and Total Diet Study

DR. SOUTH: Thank you, Nega. My name is Paul South. I am a chemist in the Office of Food Safety in FDA's Center for Food Safety and Appliance Nutrition. The title of my talk today is FDA Compliance Programs and Total

Diet Study.

What I would like to do today is provide an overview of some of FDA's compliance programs that deal specifically with chemical contaminants. Nega mentioned those are pesticides and industrial chemicals in domestic and imported foods. This includes both the pesticides program and the dioxin program.

I will also talk about the toxic elements in food and foodware and radionuclides in food; the chemotherapeutics in seafood; as well as the mycotoxin program.

In addition to the compliance programs, I will talk about FDA's Total Diet Study, which is a little different in that it is not a regulatory program but more like a general survey.

Regarding the compliance programs, the purpose of these programs is to determine the occurrence of contaminants in specific targeted foods. What we're doing is monitoring or surveillance samples and doing regulatory follow-up where required.

In addition to these compliance programs — these are done on an annual basis — we have special assignments where we can follow up on samples that we find in some of our annual programs. We can do this on an as-needed basis, so we don't necessarily have to wait until the end of the

year to look at certain issues that we have found or see that come up.

Regarding different information sources for planning samples, we actually draw information from many, many different sources. One of the most important sources is obviously our monitoring that we do here at FDA under our compliance programs that we'll discuss today, but certainly the Total Diet Study is another important source of information where we look at time trends over a long period of time for many different chemicals.

I spoke about field assignments. That's another important source of information for planning samples, as well as FDA inspections when we go into firms, not only by looking at what's going on in the firm but also taking samples at the time.

Other sources of information come from CFSAN's Adverse Event Reporting System (CAERS). This is when adverse events are reported to FDA or CFSAN. We look at this information. That could actually be an important source for targeting samples. The Reportable Food Registry (RFR) is another important source where firms are required to report certain incidents to FDA. Recall data is another important source for looking at where we want to sample next.

That is basically FDA information, but we

certainly look to other sources outside of FDA. We look to some of our other federal agencies, such as EPA. We will look regarding some of their own sampling. They do drinking water, recreational fish, and a lot of these same issues come up with what FDA does regarding, say, commercial fish. It may also be applicable to certain contaminants they're finding in recreational fish. We look at bottled water at FDA, and some of the source water for bottled water does come from drinking water sources.

As well, USDA AMS has a pesticide data program, so they are also look at pesticide issues, and we look to them for certain information. State and local governments, health departments have important information that's reported to FDA or on their Websites. So we look to some of that information as well.

We also look to other countries. CFSAN is involved in Codex Alimentarius, like many different agencies. Nega Beru actually is the U.S. delegate for the Codex Committee on Contaminants in Food, where certainly many different contaminant issues are raised each year, not only by the United States but by other countries.

We also look to other countries' reporting systems. For example, the EU has a Rapid Alert System for Food and Feed. We certainly look at that information as well.

Of course, scientific publications are another source of information, where we look for publications for contaminants in food or in feed. FDA CFSAN scientists attend scientific meetings as well. Of course, we look to academia for their publications and their work and collaborations with different land-grant institutes but also with other ag schools' food science departments.

Other sources include industry. They bring up issues with us, sometimes even voluntarily, so that we can work through different issues. Acrylomide is one important issue recently that has come up in discussions with industry.

But, as well, consumer letters that we get, receive from consumers on different issues of importance to them. And certainly Congress is another area where we gain information from not just congressmen or senators on certain issues that are near and dear to them but also some of the issues that come up through their constituents.

Today I would like to touch on some of the compliance programs. The first one is the Pesticides and Industrial Chemicals in Domestic and Imported Foods. Both the pesticide program as well as the dioxin program fall under this heading.

In regard to the pesticide program, EPA is responsible, under the Federal Insecticide, Fungicide, and

Rodenticide Act, or FIFRA, for registration of pesticides as well as setting tolerance if the use of a particular pesticide results in residue in or on food. It is then FDA's responsibility for enforcing these tolerances in both domestic and imported foods shipped in interstate commerce. The only exception, of course, is for meat and poultry and certain egg products, which are addressed by USDA.

Some of the specific factors used by the pesticide program in planning samples is the analysis of residue data. This is information that we compile every year and review every year, and certainly some of the most important information is those samples that are violative in nature, which are food samples that have pesticide levels either above a tolerance established by EPA or pesticide levels in certain foods where there is no tolerance established by EPA.

Another factor in planning samples is we look specifically at foods consumed by infants and children because this is a sensitive population group, because these children are both growing and developing, as well as because children are consuming a lot more food per kilogram of body weight.

Another factor is the toxicity and the characteristics of the specific pesticides. Certainly some pesticides are more toxic than others, but characteristics

of the pesticide itself — for example, the persistence of a particular pesticide that doesn't get destroyed in the environment, that may actually accumulate in the food system as well as in people.

We also look to pesticide usage data. When pesticides become very popular, used at very high levels, or are bought in high quantities, we will look specifically at those pesticides because those are very important.

Another factor that we look at is the dietary significance. If there is a particular product that is being consumed at high rates and there is a pesticide that is being used for that specific type of food, we will look specifically at sampling those types of products.

In regard to the pesticide program for FY15, our proposed sampling, we are focusing this year on raw agricultural foods of dietary importance. This would be foods that comprise the greater part of the U.S. diet, that in fact contribute most to pesticide exposure.

We are also targeting foods consumed in large amounts by infants and children.

Then, as I noted earlier, we will be looking at foods with high violation rates, this being foods with residue levels above or with no tolerances.

The analytes that are measured under the Pesticide Program, we actually use a multi-residue method

which looks at over 600 different pesticide residues. This is both the parent and the metabolites. We look at the carbamates, synthetic pyrethroids, benomyl, and there are just a number of different types of pesticides we look at.

We also publish annually a pesticide report. This is information (in which) we summarize in detail the analysis of the residue data. This is posted on FDA's Web site. This information actually is used widely by FDA but by others as well, including EPA, USDA, Congress, and consumers.

We've been trying to post this data as quickly as possible, but there is a lot of information under the pesticide program. Not only do have thousands of samples but we also look at those 600 different pesticides. But we have been trying to post this data on an annual basis as quickly as possible. This is actually something that people ask for quite frequently, so we've been trying to post that information very quickly.

Also under Pesticide Industrial Chemical is our Dioxin Program. Dioxin-like compounds are chemically related compounds found in food-producing animals. This is not only from dioxin and furans, which are inadvertently produced through combustion processes normally, but also in PCBs. Certain PCBs have dioxin-like activities. These were produced in the past at very high levels.

The issues with dioxin and dioxin-like PCBs are that they are very persistent in the environment, don't break down, and they also accumulate. There are certainly some issues concerning exposure to dioxin including adverse health effects, including reproductive and developmental problems, even cardiovascular disease, increased diabetes, and increased cancer.

We posted a dioxin strategy document. The goals for this program are to obtain profiles of background levels of DLCs in a wide variety of food and feed. One of the issues with dioxin is that the analysis is very unique, looking at a part per trillion. The actual analysis per sample is somewhere around $1,000. So it is a very expensive analysis. Because of the expense, there is very little information about dioxin in foods, or there has been in the past. Recently there has been much more testing of different samples.

Another goal of our dioxin strategy is to identify opportunities for reduction or eliminating contamination sources in the environment. In the past the dioxin program actually identified a source of dioxin in a feed sample. This was done through testing, where we were not only testing the aquaculture/seafood sample, but we were looking at feed as well. We actually traced this back to a feed manufacturer which was using a form of I believe

it was copper sulfate. It turned out that this was a byproduct of a smelting process in that Buffalo firm. They knew that it was high in copper and they actually sold that to a feed firm, and we actually traced that back and eliminated that. So that was one of the high points of the program.

Another goal is to provide estimates of DLC exposure because there was not a lot of information about dioxin levels in food. There was, again, not a lot of information on exposure and what foods actually resulted in exposure from dioxins.

The proposed samples for FY15. We are looking at animal-based foods, both domestic and import samples. For FDA this would include the milk and dairy products, eggs, and seafood, both fish and shellfish, including both aquaculture and wild.

Again, as I mentioned, we look also at associated feed samples for the certain aquaculture samples where we actually are at the grower collecting samples.

In addition to these samples, we look at Total Diet Study samples. The dioxin is not part of the TDS, but we do get samples from TDS shipped to our dioxin lab, where we can actually analyze these samples. By using the TDS framework, we can actually back out exposure time, the type of food, to how much food is estimated consumed each year.

Some of the analytes, as I mentioned, we look at the polychlorinated dibenzo-p-dioxin – that would be the TCDD. That is one of the congeners, probably the grandparent of all congeners. But we also look at dibenzofurans – there are 10 congeners there – as well as the dioxin-like polychlorinated biphenyls. There are 12 with dioxin-like activity.

The dioxin program is sort of a misnomer because we not only look at dioxin-like compounds under this program, but we've expanded the program to include non-dioxin-like PCBs. In addition to dioxin activity, some of the properties of PCBs, the non-dioxin-like PCBs, also have certain adverse effects on people.

We are also looking at brominated flame retardants recently. We are looking specifically at some polybrominated diphenyl ethers, six of the most common congeners that had been found in some of the brominated flame retardants used in different consumer products.

I note the strategies posted on FDA's Website, as well as dioxin levels and exposure estimates from both the TDS samples that we analyze as well as some of the non-TDS or targeted samples.

The next compliance program is the Toxic Elements in Food and Foodware and Radionuclides in Food. Today one of the components of the program is foodware, where we look

at leachability of lead or cadmium from flatware or ceramic ware. I won't discuss that today, but I will talk about the toxic elements in food and the radionuclides in food.

Toxic elements occur in food due to different agricultural practices, certainly some past agricultural practices, and industrial emissions. They also occur naturally. Exposure to toxic elements results in adverse health effects, including kidney damage, endocrine disruption. There are certain developmental and immunological disorders, as well as cancer and even death at high levels. The program is designed to monitor foods that contribute most to toxic element exposure, particularly again for the sensitive populations.

Proposed samples for FY15 include, for domestic we're looking at fruits and vegetables, milk, eggs, and seafood — again, we're looking at both aquaculture and wild — game meat, honey, and juice and juice concentrate as well as candy.

For import samples, we're looking at those same types of samples, but also this year we're looking specifically at certain spices, even those spices that are consumed generally at lower levels. We have found some issues with spices recently, and so we are going back and looking specifically at some of those.

The analytes of interest include lead and

cadmium, as well as mercury in seafood and total arsenic as well as inorganic arsenic. Those would be for non-seafood samples.

The other program under the toxic element program is radionuclides in food. The greatest potential for accidental contamination results from peacetime uses of radioactive materials, such as for generating nuclear power, both domestically and abroad. Certainly we know this. There has been the Fukushima accident recently as well as the Chernobyl. These are incidents where we see a release of radionuclides into the environment.

The goal of the program is to analyze samples to determine current levels and trends in food over time and to access dietary exposure. For the radionuclide program for FY15, some of the proposed samples include milk – this is retail samples, this is for domestic – seafood samples. We also target nuclear power plants in the country and collect samples in the vicinity of the nuclear power plant, specifically fish samples as well as bulk milk samples if a dairy is located within the area. We also look at raw vegetables and food crops of local importance.

This year we are again targeting import samples from Japan because of the Fukushima accident. This includes fruits and vegetables, rice, tea, dairy, seafood, and some of the associated products with these types of

different foods.

The analytes that we look at include the gamma-ray emitters. That includes generally the cesium-134 and cesium-137, as well as iodine-131 — 131 is generally not found because of its short half-life. We look at potassium-40, which in fact is a naturally occurring radionuclide, and ruthenium-103 and ruthenium-106.

We also look at the beta emitter, the strontium-90. When we are targeting some of the samples around the country, we also look at tritium.

In fact FDA does have guidance levels for these radionuclides. These are called derived intervention levels, or we call them DILs. They include some of those same analytes that we test for — strontium-90, the iodine-131, and cesium-134 and cesium-137.

Another compliance program is the chemotherapeutics in seafood. Certain chemotherapeutics are approved for animal drugs used for aquaculture seafood. Certainly in the past there has been an increased production and consumption of aquaculture seafood. There are issues involving drug residues found in different seafoods, including hypersensitivity or allergenicity to some of these drugs.

Another important issue that FDA is certainly concerned about is that antibiotic drug residues may also

result in antibiotic-resistant bacteria.

For FY15 we'll be looking at domestic samples including aquaculture seafood. That includes the crab, crayfish, lobster, shrimp, tilapia, salmon, and trout samples. Though this is a seafood program, chemotherapeutics in seafood, in the past few years we've been also looking at honey samples. The use of antibiotics in treating honeybees is actually an issue that has come up in the past. Certainly the health of the honeybee has been in decline, and it seems to be that beekeepers have been using antibiotics to treat honeybees, so that issue has come up.

For imports we are also looking at some of the same aquaculture seafood samples. We are also looking at eel as well as frog legs. Again, we are also looking at honey samples.

For seafood, there is a list of different drug residues we look at: chloramphenicol, nitrofurans, as well as the triphenylmethane dyes – that's the malachite green, violet, and brilliant greens, but there are all sorts of different ones. Quinolones or fluoroquinolones are used. A lot of these drugs are actually – the ones that we see most often are the very inexpensive ones used to treat different aquaculture. Because you are treating the aquaculture seafood, they use very large amounts of these.

For honey we have a very similar list of fluoroquinolones, the nitrofurans as well as the diphenicols or chloramphenicol. Those are some of the chemotherapeutics that are commonly used to treat honeybees that inadvertently end up in the honey.

The last compliance program I'll talk about is the mycotoxin program. Mycotoxins are toxic metabolites produced by certain that grow on various agricultural commodities. Environmental factors such as temperature, humidity, and rainfall can affect mycotoxin levels. So in certain years, which you could probably predict on what kind of rainfall affecting the growing period or during the harvesting period, we can see certain mycotoxin growth and certain mycotoxins in the different agricultural products.

In general, occurrence of mycotoxins is not entirely avoidable, but it certainly can be reduced by proper conditions for both the harvest and for storing.

For the FY15 samples, our proposed sampling includes domestic grains. These are cereal grains — corn, wheat, barley, rye, oat, and rice — as well as the products produced with these different cereal grains, including breakfast cereals, baby cereals, snack foods, and bakery goods. But we also look at tree nuts, peanuts, and apple juice, as well as apple juice concentrate.

For import samples, we are looking at some of

those same samples as our domestic focus, but we are also looking at spices.

This table provides an idea of the different mycotoxins we look at specifically, as well as some of those susceptible foods. In fact FDA does have action levels and guidance levels for some of these mycotoxins.

For aflatoxin, again we look at corn, peanuts, tree nuts, dairy products. We have an action level of 20 parts per billion for all products. For milk products we actually look for another aflatoxin, M1, at 0.5 part per billion.

We also look at fumonisin in corn, and we have guidance levels of 2 to 4 parts per million in different corn products.

Deoxynivalenol is another mycotoxin. The susceptible food is wheat. We have a 1 part per million in finished wheat products.

Patulin is another mycotoxin found in apple juice. There is a 50-parts-per-billion guidance level for apple juice and apple products.

Ochratoxin is another mycotoxin affecting wheat, barley, beans, raisins, and coffee. Though we don’t have a current action level or guidance level, we look at levels found on a case-by-case basis and certainly look to Codex levels when evaluating some of these levels in food.

We discussed some of the compliance programs. I also mentioned some of the field assignments that we'll do on a sort of regular basis when issues do come up. Recently there was an EU Audit Assignment. This came out of a recent audit or back in 2010 of both FDA and USDA programs designed to monitor chemical contaminants in domestically produced animal-derived products.

The audit obviously identified differences like they always do between the EU and FDA as well as USDA in the design of the respective programs. Out of this audit came a multi-year assignment that we issued back in 2012. This addressed pesticide residues, drug residues as well as industrial chemicals and toxic elements in different foods. It was basically some of the suggestions by the EU looking at milk, eggs, and honey as well as certain game meat. I guess these were products that were exported to the EU, including bison, deer, elk, and rabbit.

That was in 2012. We've had a multi-year assignment. Field assignments this year — I think we are just finishing up assignments to address EU's concerns, so we will be looking at additional samples of imported honey, both domestic as well as some imported honey. We are looking at conventionally as well as organically produced and free-range domestic eggs, as well as certain chemical residues, drug residues, in game meat, including bison,

deer, and I think we've included elk as well as rabbit.

Now we switch gears from some of FDA's compliance programs to the Total Diet Study. The Total Diet Study began, I believe, in 1961. It's an ongoing market basket study looking at various contaminants as well as nutrients in foods.

There is actually a Total Diet Study food list which represents the typical American diet. This food list is updated on a regular basis to reflect changes in what the American public is eating. For example, I think in the past recent changes were the inclusion of olive oil, and I believe we went from pan-frying fish to grilling it. So not only do the foods change but also the techniques or the processes in which they prepare the food.

That is one of the interesting differences between this type of program and some of our monitoring programs. Our monitoring program, say, under the dioxin program will look at dioxin-like compounds in salmon. Under that program will be the salmon comes in as a filet and they will simply extract the sample as a raw sample. Under the Total Diet Study, how they prepare the samples is how you would traditionally eat it at home. So there actually a process by which salmon would come in and it would be grilled, and that sample would then be analyzed. So anything that might affect the fish by preparation will

be reflected in what we find the Total Diet Study samples.

For the salmon, most people, unless it's smoked salmon, don't eat salmon raw. For the dioxin program, you may be getting results that may not be necessarily what people are consuming. You could be losing fat, which could result in a reduction in some of the dioxin-like compounds.

In the Total Diet Study, because the samples are prepared as eaten, you are actually seeing exactly what the consumer would be eating. That's the importance of this program. What it is designed to do is actually look at the dietary exposure of certain contaminants as well as nutrients.

The purpose then is to determine background levels of contaminants in a wide range of foods. What we do with the Total Diet Study is use the results, the exposure estimates, to focus resources for the FDA compliance programs.

TDS exposure estimates indicate potential risks and identify main dietary sources. It is in the compliance part where we can go back and collect specific samples.

Under the TDS there are four regional market baskets collected each year. Within each regional market basket there are three cities where 280 foods are collected, or ingredients for foods are collected. These samples are then sent to our Kansas City laboratory where

they are actually prepared for consumption. The three samples from each region are then composited and analyzed.

For example, in the Northeast you would have three cities, like Buffalo, Philadelphia, Portland. Those three cities would send samples together. Those would be prepared, then composited, and then analyzed. That would be one market basket. Then we go around the country and do four market baskets per year. So there is quite a lot of work done on not just the analysis of samples but also collection and preparation of samples.

The TDS food lists. These are the samples that actually are used to represent the U.S. diet. It includes major components of the average American diet. It is based on national food consumption survey results, such as NHANES. It is limited to foods that are available nationwide, so that when we send collectors out, we can actually get the sample and have it come back and we are confident that we will have a sample to analyze. Again, the food lists are revised periodically to reflect changing dietary habits.

This slide provides a list of the different food types: dairy, eggs, meat, poultry, fish. Again, FDA doesn’t regulate meat, but we do include TDS samples that contain meat so that we get a picture of the whole diet.

Fruits and vegetables, mixtures. For mixtures

you could have all sorts of different sandwiches. They will actually collect sandwiches at Subway or McDonald's. Fast food, like a hamburger is also collected, so there are also different samples that really actually represent what people are out there eating.

The analytes that we look at for each TDS food. There are over 600 pesticide residues. We look at the industrial chemicals, including PCBs. Radionuclides are also looked at; elements including the toxic, and nutrients.

TDS foods also are analyzed under other programs. So even though an analyte may not be included under the TDS analytes, compliance programs use regularly TDS samples to look specifically at a contaminant under their program. The beauty of the TDS samples is that they are actually linked to diet. The consumption can be backed out, so exposure estimates are very easily obtained using the TDS methods.

What really needs to be emphasized is the TDS program generates greater than 20,000 data points each year, so not only the preparation but the amount of data that is generated is incredible.

But again, the role of TDS, it is a time-trend survey. It has been going on for years. So there is the ability to look at chemical intake over I think since the

1960s. So we have very interesting plots for different toxic elements.

For example, for lead, if you look at the data, you can actually see where there has been such a reduction in practices, such as the use of lead-soldered cans, which was outlawed by FDA a number of years ago. Over the last few decades, you'll see that actual lead intake has gone down incredibly.

Again, to emphasize, TDS is not to enforce regulations though. If we do find something, we can go out and look at samples as a result of TDS findings.

Results for TDS are used for monitoring the impact of regulatory actions; for example, the banning of lead-soldered cans. You could actually see that reduction in lead consumption.

It is used to identify potential health hazards as well as provide support for risk assessments and international food standards. There is incredible international importance for TDS. Total Diet Study does not just occur in the United States but other countries have this throughout the world.

This past year, TDS results were submitted to WHO, the Geographic Environmental Monitoring System. The food database, this was to aid in the work of a Codex committee, the Codex Committee on Contaminants in Food.

They were reviewing maximum levels for lead in different foods. The TDS program as well as FDA's other compliance programs submitted 12,000 data points last year to aid the international development of these new standards or revised standards for lead in different food products.

The data is also important for international risk assessments, such as for the joint FAO/WHO Expert Committee on Food Additives, as well as the meeting on pesticide residues.

WHO actively promotes TDS programs worldwide. FDA was involved in the first international workshop for promoting TDS work in other countries. Our TDS experts were involved in these workshops as well as different training programs.

Recently the TDS has been rebuilding. We have included more staff and more capacity. What we would like to do is actually post data more efficiently and have this data on our Website available for folks to look at for other countries, for consumers, for academia, for research.

We have also been evaluating the sampling protocol. We have updated the food list recently to be more representative of the U.S. diet. We also are improving the Web content as well as the presence so that it is more obtainable, so that people can download this data easily and efficiently.

With that, I would like to end. Hopefully, I provided a background on some of the compliance programs as well as TDS.

I think there's a few minutes for questions from the advisory committee.

DR. HAYES: Thank you, Paul, for that really nice overview.

Agenda Item: Clarifying Questions

DR. HAYES: We now are open for questions. I think we will start with Walter Willett.

DR. WILLETT: I don't know if this is the time for specific questions, but I was wondering, in TDS, I think you monitor trans fat, do you not? You've had a couple of reports on that recently?

DR. SOUTH: I believe we do. The Total Diet Study, I believe trans fats are a component of that, though to be honest it's not actually what I do. I look more at contaminants, so the trans fat aspects of the TDS, it's not something that I actually have gotten into.

DR. WILLETT: Maybe somebody else has more information then.

DR. SOUTH: The Website would provide all that information. There are links to the TDS. It describes each and every analyte as well as some of the posted data that's available, so that information is available on line.

DR. WILLETT: Another question about that was sodium. Obviously, these are the things that are probably the biggest health threats, rather than the contaminants.

DR. SOUTH: Sodium, I think that is one of the elements that actually is listed, is one of the analytes, and you could actually obtain that from the Website.

DR. WILLETT: Another issue that has come up — maybe this isn't quite the right place; I don't know where it fits — but fiber intake. I have been troubled recently looking at food labels of products being advertised as high fiber. You look at the ingredients and it's cellulosic fiber, it's like cardboard, not from food, and that is pretty troublesome. Is that something you're monitoring?

This gets into definitions of what's allowed on these claims for fiber and things like that. I know it's getting a little bit overlapping.

DR. SOUTH: Unfortunately, I am not — in regard to TDS, I actually deal more with the chemical contaminants, but I am sure we could direct you to who deals with different types of fiber — insoluble/soluble fiber — as well as the labeling requirements on fiber. But to be honest, I really cannot answer. I don't deal with the fiber issues very often. In regard to TDS, I usually deal with some of the chemical contaminants. But that information I certainly can provide to you. Whatever FDA's

resources are, we can certainly provide that kind of information.

DR. WILLETT: To go back to chemical contaminants, I noticed in that long report on the very last page there were some evaluations of mycoestrogens that are used for growth promotion. I wondered, we've learned in human studies that the progestins are actually much more dangerous for breast cancer in particular. I believe some of those are included in growth-promoting packages. Do you monitor those?

DR. SOUTH: Actually, I look at industrial chemicals. I am not sure what we look at in regard to that, but again, we could provide that information for you at the break, and then we can certainly find out what exactly that you study and what we actually do monitor in regard to that.

DR. WILLETT: Okay, great.

DR. RUZANTE: You mentioned a couple of sources and also some of the factors that you consider, from what I understood, when trying to identify the products that you're going to test as well as the chemical compounds.

I just did not quite understand if there is a systematic approach to incorporating those to arrive to the decisions of, okay, we're going to test for those products and we're going to test for those chemicals, contaminants.

I just did not quite understand the process behind arriving to the conclusion, oh, we're going to test for those. So if you could explain.

DR. SOUTH: You will see in these next presentations where CFSAN has, through FSMA, and where we will be looking at risk ranking and risk modeling, we are incorporating that kind of information more and more into what we do now.

In the past we've looked at lots of different sources and trying to envelop those kinds of technologies. But I think Mickey can certainly include some of that discussion on those kinds of sources that we look at.

DR. RUZANTE: But right now, for example, you would say that — I understand that you have all those tools, but at this point right now, those decisions on what you look for are sort of an ad hoc, I guess we would say — is that correct to say? You are already incorporating those tools that FDA has developed to make sure?

DR. SOUTH: We work, again, with different agencies in regard to risk for different chemical contaminants. We'll look for reference doses, we'll look to EPA for some of the references doses for some of the chemicals. If in fact we are seeing certain chemicals that have reference doses, our risk assessment group will look at the levels of the different chemicals that we're finding

to determine whether or not this is actually an issue that's coming up.

Some of those certain sources that we include, they do incorporate some of the risk-ranking procedures. But I think what we are trying to do now is formalize a process by which we do that kind of ranking. Certainly we have included that in the past, but I think now we are providing the actual standard operating procedure for doing that.

But again, I emphasize there are a lot of different sources from which we get the different information.

DR. RUZANTE: Sure. I do have two other questions.

On your sampling plan, I didn't see any numbers of how many samples you are collecting. I wonder if you could provide some background on what you are expecting to — I understand that the major goal of those programs is to detect violations, not necessarily determine the prevalence of those contaminants out there in the population, let's say. So what are the parameters you're using to design your sampling? Do you have an expected rate of finding? Could you provide those parameters on how you design in regard to the sample numbers?

DR. SOUTH: I didn't include sample numbers

because we're still looking at it. That was for the FY15. But in the past we do look to our statisticians to determine the N that would give us significant findings.

Again, to actually do a survey that is statistically significant requires an incredible number of samples. In the past, for our pesticide program, we actually did look specifically into trying to determine how samples it would be to look at for a specific pesticide, and I believe we were at 800 samples import, 800 domestic, for a single pesticide in a single food. So it is very difficult actually to get some of these statistically generated results for so many different contaminants in so many different foods, especially with the limited resources we have.

But we do work with statisticians when issues do come up to try to determine from past results, past findings for that contaminant in that type of food, how many samples it would take to determine whether or not there is an issue.

For some of these compliance programs, when we do see a problem, what we will do is actually target a specific country for a specific food and go back. The point of it is really to find some of these problem foods where we have issues with certain chemicals that can be either addressed or simply not approved, or we will reject

them at the border.

DR. RUZANTE: My final question is about — you mentioned NHANES as one of your sources of consumption data and driving. You also mentioned when you do the TDS, you update regularly. If you could be more specific about what regularly means — because that can be very relative. Also, if the update is based on NHANES, because NHANES can be quite old, I guess.

Also, you mentioned dietary significance. I was also trying to understand how you determine dietary significance, if this is also NHANES-based. Anyway, if you could tell me a little how you use the data.

DR. SOUTH: The Total Diet Study, what they are using are surveys for consumption data for different foods. The idea is that we can generate from the consumption data. First we need to identify the food that actually represents what is being consumed. The NHANES data will provide an estimate for a specific Total Diet Study food that is being consumed so that we can determine how much food — we have the amount of food that's consumed and the amount of the contaminant to back out what the dietary intake of the contaminant might be.

So we use the best available data. NHANES is one. As you said, this data comes in — they have different surveys, and some of the survey data is older. But I think

NHANES is only one of the types of survey food consumption data, and we will use just about any different sources. It may depend on a particular food. If there is an issue with a particular food for some contaminant, we will look not just to NHANES but to other surveys that actually have that type of food included.

In regard to how often we post the data for TDS, my last slide I believe was about TDS and how we're trying to revitalize the program. There is a delay in posting the data because —

DR. RUZANTE: I am sorry, it wasn't posting. You mentioned that the TDS gets updated. So I understand like you're adding new, updating and removing the food lists.

DR. SOUTH: Oh, the food lists. Exactly.

DR. RUZANTE: I want to know how frequently you update this.

DR. SOUTH: Right. Again, I am not the Total Diet Study expert here, but I believe they update the food list every few years. It's sort of dependent on if there are changes in the diet and what specific foods are included in the diet. If there is a particular food that is falling out and no longer consumed, they will replace that with a food that is so that they can go out and collect that same food, if the availability of the food — but generally, I think the food list may be updated every

few years, but I would think every 5 years, I believe. I'm thinking back, but again, I am not the expert on the Total Diet Study.

But what they try to do, obviously, is to include foods that are consumed at a high level that can represent what the diet is for the different people represented that are eating the food.

I didn't mention it, but we do have different subcategories. There are 14 different age/gender groups as well as a total population. What they are trying to do is include foods not just for the average population but also for each one of those different age/gender groups as well. Does that help?

DR. RUZANTE: Yes.

DR. HAYES: I think the specific answer you are looking for is in some of the questions that we have. It was just pointed out it is 10 years, if this information is correct, every 10 years approximately.

DR. SOUTH: Okay. I think that is probably sort of an average.

DR. ARMBRUST: You brought up one of those factors that is going to be important in any risk-ranking process is chemical occurrence in the particular commodities. Therefore, data of occurrence is going to be critical.

You've got the Total Diet Survey, which is generating some information on, for example, pesticides in particular commodities. You also mentioned the USDA's pesticide data program, which is through the Agricultural Marketing Service, AMS, which is also run in accordance with the Microbiological Data Program, MDP.

As you are probably very well aware, the funding for those has been severely cut back in recent years, and those programs therefore have been shaved back considerably as well. I saw those programs also mentioned as particular data sources that you were using for these. With those programs going away, do you anticipate that potentially as a big barrier in generating some of this occurrence data?

DR. SOUTH: Certainly looking at that data is a source of information for us to target our resources, and not having that information, finding some of the results for certain pesticide levels in certain commodities from certain countries, that can actually obviously be a barrier to us in focusing our resources.

But again, that's only one of the sources of our data. We use whatever is available. The PDP data actually in the past has been an important factor, and we'll use it to the best of our ability. But again, we have different sources for data, and we will try to exploit whatever is available at the time.

DR. ARMBRUST: But the more data —

DR. SOUTH: Obviously, the more data, the better, exactly. A reduction in sample information from them obviously could be a barrier, but again, we have different sources for our data. What we will do is try to exploit other resources that are available.

DR. ARMBRUST: One other question I also had was you mentioned as a way of targeting sampling, especially for compliance programs, was pesticide use. Now, the only state that generates consistent pesticide use reporting is California. No other state generates that. So are you basing most of your pesticide use primarily on crop coverage? That is generally the way USDA has done it.

DR. SOUTH: That would be exactly one of the ways that we would use that. Any data that is available, but we are talking domestically but also internationally. Wherever we can find information about the production of a particular pesticide and what country it's being used in, if there's higher use of a particular pesticide in a different country and that data is available, we will actually target that country for that specific commodity, looking for that particular pesticide.

But, correct, with the state data, we would use that data if it's available.

DR. ARMBRUST: The last question I have was

concerning – I think you mentioned for pesticides part of this was based upon risk, and I was wondering how much of the EPA you were using, because obviously under the Food Quality Protection Act it required aggregating risk assessment across pesticide classes. Are you guys using that as a basis also and incorporating that into some of your prioritization?

DR. SOUTH: Absolutely, the information generated – EPA is the one that looks at the risk of some of these – well, they set the tolerances, so we look to them for some of that information. The tolerance itself will determine some of the risk involved with a certain type of pesticide. We would look to some of the information generated by EPA on some of the toxicity of certain pesticides. So yes.

DR. SWAIN: I think it makes good sense, of course, to sample food and food mixtures after they've been prepared for consumption, after processing. Could you provide any additional information as to any challenges in terms of sampling food mixtures, in terms of controlling over multiple samples, in terms of the point of sample within the food matrix and how that may influence the data?

DR. SOUTH: In regard to food mixes, the Total Diet Study, because there is actually a preparation of different food mixes – for example, there is actually a TDS food called spaghetti and meatballs. Actually, they will

produce a spaghetti and meatball dinner and then it will be that sample that is composited and analyzed.

If you are looking for a specific commodity or a specific contaminant in that spaghetti and meatball, it would obviously be very difficult to figure out which ingredient provided was the source of the issue.

In the past with TDS, we can go back and look at specific information about different ingredients used in the product, but it does get very cumbersome. The food labels now actually are scanned, I believe, so that we can go back and look specifically to the type of food that was used, the label, a lot number.

But for this particular program, because it's sort of a survey, it's not necessarily regulatory, actually going back to finding the source of a contaminant is quite difficult for some of these mixtures.

DR. RANGAN: I am going to try to talk.

Just to follow up on Kevin's question, does FDA receive any pesticide reporting data from the industry at all? I am curious about that.

DR. SOUTH: I don't know exactly what information, what type of information —

DR. RANGAN: That would be a great question, if someone could answer that at some point.

DR. SOUTH: Yes. I can go back and try to find

that answer for you.

DR. RANGAN: Thank you. Like drug reporting. I am curious if you guys get any pesticide info.

Regarding guidance action levels, do you have any set for the chemotherapeutic drugs that are used in foods, like you do for radionuclides?

DR. SOUTH: There are actually residue levels set. They are established by CVM. That's our Center for Veterinary Medicine.

DR. RANGAN: Are those posted on line?

DR. SOUTH: I don't know where we could find those, but I could certainly try to find that information for you.

DR. SOUTH: That would be great. Thank you.

DR. SHREFFLER: I just noted that one of the five categories of chemical contaminants in human food is allergen. I haven't heard anything about that. Can you comment on whether that's part of the scope of the total food? That's probably where it's most relevant, the Total Diet Survey.

DR. SOUTH: Regarding allergens, I am not sure if that actually is one of the analytes. I don't believe it is included under the Total Diet Study.

DR. SHREFFLER: Or anywhere else, in terms of surveillance?

DR. SOUTH: Is that part of the program today, the allergens? Mickey, are you addressing that?

DR. PARISH: I will do that.

DR. SOUTH: So Mickey actually will talk about risk ranking for allergens.

DR. SANTERRE: I would like to ask two parts of this question. How well have we learned from the past? In 2008 we had melamine pop up in our foods and that surprised all of us. How much exploratory assessment work do you do where you're not looking for targeted analytes but you're basically on a fishing expedition?

DR. SOUTH: Well, with the limited resources, knowing what's out there and what's going to happen next, though we do actually keep a good eye on other countries, what they are finding, other issues that occur, such as the melamine issue. Whether that was something that could be predicted or not, whether that was something that was going on at the time or whether we should have predicted something like that and had been testing for it, I don't know.

But we certainly keep an eye on — with all those different sources, some of the other issues that are going around globally — so in fact if it's happening in another country or is an issue elsewhere, we certainly look. That is one of the factors that we weigh in on looking at

different contaminants in different foods, on focusing our resources.

DR. SANTERRE: So we have about 8,000 industrial chemicals. I know you listed it as a category, and we probably have about 2,000 industrial chemicals that could be a food problem. So it seems like we need to spend a little bit of time looking for those things that we don't expect, whereas you've described today things that we do expect.

The second part of my question is in 1999 in Belgium and in 2010 in Germany, we had big outbreaks of PCB getting into industrial oil that was fed to animals. Have we put in place anything to catch that here? You described doing dioxin tests for about $1,000 per pop. We've demonstrated that using screening tests we can screen for PCBs at maybe $25 per sample in fish.

Is there any kind of strategy to screen samples — in this case it would more feed-related — to try to catch those things? It took the Germans probably from March to December to catch PCBs in their products. Do we have anything in place to catch those things that keep recurring?

DR. SOUTH: That is a good question. Actually, with regard to dioxin, because of the cost of the test, we did look to the use of a CALUX method. It is done on a 96-

wall plate with a cell culture. Just as you alluded to, the dioxin issue affecting feed, it was our Center for Veterinary Medicine that actually started working with a manufacturer of the CALUX method so that they could in fact screen different products very quickly to determine whether or not there is any D-luciferase(?) enzyme, the reaction in which a particular feed component could then be analyzed using the high-resolution mass-spec method, which is the $1,000 method.

So we have looked into these other methods not only as a cost saving but also as a quick method for looking very quickly at different types of feeds and feed components, which obviously end up, because they are lipid soluble, in the lipid portion of the food.

So that is exactly one issue that we've looked at in our laboratory. Again, there are some difficulties. It's a cell culture method which is a little different from what these physical chemists work on all the time. So having a separate laboratory with growing cells and keeping cells alive, they did experience some difficulty with that.

But that is exactly the approach that we wanted to take and have been taking with dioxin because of the expense of the high-res method that we would screen feed samples, as well as food samples, for dioxin. So that is worked into our protocol as some way of addressing the cost

and the time it takes to analyze a sample for industrial chemicals.

DR. SANTERRE: I guess I would finish my questions just saying that I think we should spend time looking at where we've had outbreaks or incidents in the world in the past and see if we're prepared to catch those and prevent those here in the United States.

DR. SOUTH: Sure. The Center for Veterinary Medicine actually has a program for looking specifically at food and feed components. Like you said, one of the issues, this year they are actually doing a field assignment to addressed rendered fats, which could in fact address a contamination event using a PCB oil, transformer oil, or oils that get recycled.

That issue obviously is an important one because finding out that you have transformer oil in your feed oil, the reasons why the Belgians found out was only because the eggs were cracking and they had to work back to determine why the eggs were cracking, and they found there were high levels of dioxin in the eggs that people may have been consuming for — it was unclear exactly how long that took, but obviously that was a big event that affected the whole government.

DR. ROSS: My question also concerns the Total Diet Study and the idea of prioritization or signals. It

is notable here that the study has been going on for something over 50 years and has increased from 82 foods up to 280 now, so definitely it has expanded.

My question is, do you make use of data that has been collected over time? Do you make use of trends or statistical analyses that might be helpful? For example, are there certain contaminants or nutrients that don't vary much by region or that don't vary much over time, and is there a way of using this information to focus the resources on the most likely or most changeable or most interesting components?

DR. SOUTH: I know that part of the revitalizing was to add FTEs to the TDS staff to look, just exactly what you're talking about, to look at data over a number of years and to use the data that we have. We have certainly tried to do that in the past, and I think that is also the approach that we're taking now and to use the data even more than we have in the past to try to identify those certain contaminants that may be an issue that we just haven't addressed using the data we have.

But certainly I think that's the approach with the recent revitalizing of the TDS program approach.

DR. ROSS: Thank you. My suggestion really had to do both with your focusing on things that might be signals or might be important but also perhaps

consolidating or simplifying those that could be looked at less.

DR. HAYES: We are into our break time, but we still have a number of questions. I am going to continue with the questions and just cut our break short.

DR. MCBURNEY: Thank you very much, Dr. South.

My question also is about the TDS and prioritization of resources. As I understand, you are looking at the food basket in essence based on what consumers are choosing to eat. You are analyzing it. Trends will happen in nutrition because people are changing their food behaviors, and you are also changing the method of preparation. So that will influence the nutrition content.

But in the residues of pesticides and those others, do you prioritize in terms of how and what you will analyze, say a seafood, a salmon, which would be different than the pasta or than a cereal base, because you would expect differences? Or does everything get everything in terms of an analysis?

DR. SOUTH: I believe we've actually adopted multi-residue methods for pesticides. So I believe the multi-residue methods will look at all pesticide residues I think similarly, so you would be looking for all of them all the time, I believe.

But again, I don’t know the TDS pesticide — but I think because we do use multi-residue methods, I think we’re generally looking at all different pesticides all the time.

DR. WALLACE: Thank you, Paul. I really appreciate your adding some overall context to this stack of papers. I appreciate now the details better.

I just want to make sure that I’m clear. I think this is what you stated, that the compliance programs that you described are designed as a monitoring program, monitoring exposure, and not necessarily monitoring risk. That to me is a very important distinction from what Erik’s presentation — again, it was a very nice presentation — is that you're conducting this program, I think you said, or someone at the table said, for enforcement? But I also think that would also be for informing the risk-based decision making that Erik talked about as well.

By that I mean if your results continue to come back saying that exposure is minimal, then that would inform the risk-based decision making, and those chemicals’ analytes may drop off the table. That’s my first question or comment. Is that correct?

DR. SOUTH: Well, they are regulatory in nature in that we’ll be looking at samples over the period of time. Anytime we see any results that come back, we look

at chemical contaminants on a case-by-case basis if there is no level established, but we do provide that to our risk-assessment staff, and they will look specifically at the levels found in the foods, look specifically at what is consumed, what the level is that's found, and determine whether or not there is an issue, if there is going to be a regulatory action against the product.

DR. WALLACE: So it's an iterative process between the —

DR. SOUTH: It is. The data is not just stagnant. We don't just put the put the data away. This data is accumulated and reviewed by the risk-assessment staff on a regular basis.

DR. WALLACE: A couple of other questions if I may, Chair. I know that you're trying to do your job and hold us to the timetable.

But let's talk about the dioxin/furan program. I appreciate the fact that you said that it's a misnomer because the chemical class is much broader than that. Could you tell me what the criteria are for inclusion of chemicals in that program? Is it based strictly on reported biological activity or are there some structural restrictions as far as whether a chemical is included there or not?

DR. SOUTH: We have a single lab and we are

trying to expand that. Initially, it was simply for dioxins and furans. Part of that was because the methodology is very complex, and in fact, because there are toxicity equivalents for these certain congeners, and they all had dioxin-like activity, it was basically viewed as a dioxin program.

We then expanded the program to include dioxin-like PCBs. That was in addition to the dioxins and furans. Again, part of that was because we were looking at dioxin; it was a dioxin laboratory.

DR. WALLACE: But now it is expanded to include the brominated diethyl ethers? Would polybrominated biphenyls be included? Is the class strictly limited to aromatic compounds, or would some polyhalogenated alkanes fit?

DR. SOUTH: Currently our methods and what the actual laboratory can analyze for are polybromide diphenyl ethers. That was a class that a number of years ago, the fact that these were persistent, there was definitely a lot of concern about the use of these in consumer products, not necessarily because they were just in the food but because there were high levels found not just in nursing babies, but also there were high levels found in the United States. They were trying to determine what the issues were.

We included the polybromide diphenyl ethers, this

brominated flame retardant. Obviously, one of the reasons was because of the incidence of this in breast milk as well as the amounts that were being used by the industry as flame retardants in consumer products. But I think part of the issue was that we wanted to get a feel. There wasn't a lot of information about polybromated diphenyl ethers, and we wanted to simply find out what was being found in food products in the United States, and it was a method that could be adapted to the dioxin laboratory.

DR. WALLACE: Very well.

The other point I made, and I think Catherine alluded to this, and that is that when you're doing a screening study for dioxin, as an example, that tests out at $1,000 per sample, is it necessary to hit parts-per-trillion levels in a screening protocol? Or is it sufficient to hit whatever the tolerance level is?

DR. SOUTH: What we were discussing earlier was the use of a CALUX method, the cell-based method, so that we don't necessarily have to go to the parts-per-trillion level.

But certainly with dioxin, unlike some of these other industrial chemicals, a part per trillion, even though it seems like a really low amount, they are highly toxic. TCDD is considered one of the most toxic chemicals out there. So even having a part per trillion or two parts

per trillion can increase risk. So having a part per trillion, it is actually very important to know that.

DR. WALLACE: I am going to ask the same question in a different matter. In your testing strategies, what do you set as your detection levels? Is it the tolerance level or is it your ability — is it the minimum detection level that you can achieve?

DR. SOUTH: What we are basically looking for is outliers with the dioxin program. A part per trillion again is something important to know.

DR. WALLACE: Let's look at your brominated diphenyl ethers as an example. Let's get away from dioxin. So when you set up an analytical screen for that, do you set it up with a detection level that will achieve what is determined to be permissible levels, or do you set it up to detect as much as you possibly can?

DR. SOUTH: Oh, okay, certainly. It would be outliers or a permissible level. We are not going to try to get as low as possible just for the sake of the instrument can do that.

I think that's part of the issue with the CALUX method. Again, like you said, it is not necessarily that we need to see down at a tenth of a part per trillion. What we want to know is whether or not there are levels, and then we would follow that up with a high-res method

that would look, if we saw something that was of interest to the screening method.

DR. WALLACE: My last question, and it's probably to the whole table. You described that in each of the four regions for the Total Dietary Study, you select three cities from which you sample. Is there any reason around this table that one would suspect that the average diet of somebody living in a large metropolitan area would be a good surrogate for somebody who is living in a more rural community? Or should we be selecting cities that cover the entire region and not just the major metropolitan areas? Just a question.

DR. HAYES: Let's hold that question for people to think about.

DR. LINKOV: Very briefly, since I am the last one, you mentioned difficulties in developing statistically based sampling design, but it's a crucial issue. Juliana and others mentioned the importance of that.

Are you considering other ways to have scientifically based samplings, like Bayesian methods or decision analytical tools? And to what extent are your statisticians working on this?

DR. SOUTH: With the sampling, for both the programs we've gone to our statisticians to determine whether we can actually find a statistical difference

between samples collected, as well as the number of samples that we need to use for our sampling. We try to use our statisticians as well as we can, using the resources we have.

But in the past we have looked at statistical methods to look at the pesticide program and have seen that in fact some of the looking at different pesticides, the number of pesticides and the number of foods that we're looking at, that it would be very difficult to get the resources to look at individual pesticide levels for foods.

But we do look, we work with our statistician team to determine what methods and the actual sample size needed to find out if there is an issue with a product.

DR. HAYES: I have blown my job as chair. We have lost our break, but I think the questions were well worth doing it. But if you'll notice on the agenda, we were only allowed 5 minutes for questions, and it was such a good topic, and I think you did see that there was a lot of interest and a lot of good comments that were made.

We've got about 2-1/2 minutes before we crank back up, so if you want to stand up, stretch your legs, we're going to crank back up at the allotted time of 10:15 with Mickey. Paul, are you going to be around the rest of the day?

DR. SOUTH: I will. Probably this morning I will

be around.

DR. HAYES: But we will be able to bring you back if we need you in the course of our deliberations?

DR. SOUTH: I believe so.

DR. HAYES: All right, so stretch. You've got about less than two minutes now.

(Brief recess)

Agenda Item: Overview of Current Approach to FSMA Section 10 Performance Standards

DR. HAYES: We will turn the podium over to Mickey, who is going to bring us up to date on Section 104, the Performance Standard.

DR. PARISH: Good morning, everyone. My name is Mickey Parish. I am senior advisor for microbiology in the Office of Food Safety at CFSAN. I have been with CFSAN about 5 years. Prior to that I was chair of the Nutrition and Food Science Department at the University of Maryland and prior to that was a professor at the University of Florida for 20 years or so.

Today I want to give an overview of our current approach to FSMA Section 104, which is titled Performance Standards. Now, FSMA Section 104 is a relatively short section of FSMA but not unimportant, I will point out, and requires the agency to determine the most significant foodborne contaminants, then engage in discussions about

appropriate rules and guidance documents related to those contaminants.

Now, it is so short that I am able to actually bring it to you. This is part (a) in Section 104. I will point out that when I was teaching at the University of Maryland, teaching food regulations, I would tell students, if you're going to look at the CFR, always look for the subject, the verb, and the object, because the regulatory language can be a bit confusing.

So we've done that here in red. Basically, section (a) requires the Secretary to review and evaluate data and other information to determine the most significant foodborne contaminants.

Now, although we have not made a decision on the definition of contaminants, it should be noted that we would not consider approved food additives to be a contaminant. We did have that discussion that I will mention briefly later on.

In section (b), very simple: The Secretary shall issue guidance documents or regulations. Now, this is based on our efforts in section (a), where we are determining the most significant foodborne contaminants. It should be pointed out that these guidance documents or regulations really are addressing specific products or product classes, and, where appropriate, for both food for

humans and food for animals, and they are not to be facility-specific. In other words, we can't go picking on any one particular facility or one particular company. This actually has to be general and broad.

I did not provide the text for sections (c) and (d). Basically, section (c) requires the Secretary to coordinate activities with USDA to avoid duplication of efforts. I will point out that in part of what we've done already, we have been involved in discussions with FSIS.

The final section, 104(d), simply requires the Secretary to periodically review and revise the documents and rules that are generated under part (b).

As you can imagine, there are some obvious questions that pop up from this section. Three questions come to mind immediately for me:

What is meant by performance standard?

What is meant by most significant foodborne contaminant?

How do you determine what a most significant foodborne contaminant is?

The statute does not provide criteria for that determination. We were sort of given some free rein here to look at this and peruse and try to come up with what we think is the best method to do that, unlike Section 204 — and Yuhuan is going to talk about that — where they were

given specific criteria to address.

So when we think of performance standards, what are they? If you look in the risk literature and other literature from the ICMSF, Codex, and others, you are going to find that there aren't really good definitions of performance standards specifically. We can find definitions of microbiological criteria, performance criteria, food safety objectives, performance objectives.

So when we think of performance standards, the thought that we have is that a strict interpretation is that this is simply setting tolerances or setting action levels, or setting log-reductions, such as a 5-log reduction in juice, which our juice FASEB rule does set, or endpoint targets for hazards in foods.

A broader interpretation is that this section of FSMA actually requires FDA to engage in activities to inform risk-prioritization efforts across the Food and Veterinary Medicine program, which could include, of course, tolerances — setting tolerances and action levels, et cetera.

So FDA has taken a broader interpretation to provide flexibility to address things such as model development, sampling and surveillance, prioritization, also looking at resource allocations, et cetera.

Some guiding principles that we've used in this

activity are: to utilize objective public health data when available, to ensure that this is a science-based activity, to seek public input, and ensure that it's a transparent process.

You might have noticed in Section 104(a) that it does mention the Food Advisory Committee there; that one of the things that we are to do is to engage with the Food Advisory Committee in helping us with this activity, and that is a part of what we're doing today. We are also engaging with others as well.

We are not at a point yet, since this is a relatively new activity for us, where we have yet sought public input, but that is part of our future in how we're going to approach this.

As I mentioned, 104(a) requires us to "determine the most significant foodborne contaminants." Now, FDA has interpreted that phrase as equivalent to contaminants having significant public health impact. Recognizing that there could be variability in determining significance and that there is, of course, variability, we have taken a risk-ranking approach to this activity.

Some of our early discussions actually addressed that we need to use our activity to address both human foods and animal foods. We also finally decided, after a lot of discussion, that we were going to divide this into

microbiological contaminants and chemicals and allergen contaminants as well. Part of the reason for this is the fact that we have a database at CDC which has a huge amount of objective numbers related to illnesses from pathogens, and we don't have a similar database necessarily for chemicals and allergens.

So, therefore, based on that, we took an approach where we're going to do an objective analysis of the data that exists at CDC and take a slightly different modeling approach with chemicals. The ultimate goal here is to come up with rankings that would be for food/pathogen pairs and for chemicals.

We started off with the microbiological contaminants. We thought that would be the easier way to start. That was not necessarily the case, but we started that way anyhow. To address these contaminants, we relied on a dataset provided by CDC that gives the attribution fractions for all pathogens in the 14 food categories that are tracked by CDC and are regulated by FDA.

The starting database was provided to us by CDC through the Interagency Food Safety Analytics Consortium. This is a group, a tri-agency group, between CDC, FSIS, and FDA, that meets on a regular basis to address analytics issues and has been addressing to a large extent for the first few years now attribution of various hazards to food

commodities. It is a very active group. They do a lot of good work. So the starting database was provided to us.

The goal of the analysis is to rank the pathogens within food categories based on their medical costs and based on the loss of quality-adjusted life-years, as analyzed by our economists in CFSAN. So our economics have developed analytical procedures to monetize what a case of pathogen illness costs. They have engaged in this activity for the economic analyses that have gone into our rules thus far, the Preventative Controls Rule, the Animal Controls Rule, the Produce Rule, and others. So this is a recognized analysis that they've been doing for a number of years.

We believe that the results will show the financial impact due to each pathogen/food pair. Based on these analyses, we ended up with 107 pathogen/food pairs that we were able to look at.

Again, the CDC represents an objective database of information. They provided to us, again, the numbers of illnesses which they estimate annually for each pathogen and food pair for which they have information. I will just point out that this is based largely on data that was published in the Scallan, et al, paper from 2011 which estimates the numbers of illnesses, hospitalizations, and deaths per pathogen, and the Painter data that was

published I think in 2013 — maybe it was 2012, I think it was 2013 — which gives specific fractions for the pathogen/food pair combination.

The specific commodity groups which CDC follows, which we accepted their data, basically are broken down into animal-based foods and plant-based foods. You can see them listed here: finfish, crustaceans, mollusks, dairy, eggs, and game meats for FDA. Many people don't recognize that FDA does regulate game meats as opposed to FSIS. And the plant-based: grains and beans, oil and sugar, fruits and nuts, fungi, leafy vegetables, root vegetables, sprouts, and vine-stalk vegetables, such as tomatoes.

One issue that we will have in the future, since we are required to repeat this activity, or come up with the ranked list every 2 years, is that these commodity groups have been expanded by CDC, FSIS, and FDA to include additional commodity groups. For example, now there is a separate fruit group from the nuts group. So that is one obstacle we are going to have to address in the future when we repeat this.

These are the 22 pathogens that were in the CDC database. I will point out that we did include marine biotoxins in this analysis. We believed that the fact that we had hard objective data, as opposed to the chemical contaminants group where we don't have so much objective

data, gave us the opportunity to look at this particular group of toxicants in an objective data-driven manner. So we were able to do that, and we did.

We have gone through and done a basic analysis. All the results that we have are very preliminary, so we are not sharing those. There are still internal discussions on what the results mean. As you can imagine, some common ones that you would expect to pop up at the top have popped up.

In terms of the animal food and feed pathogens, we looked at the ability of a pathogen to cause illness in animals. We looked at the ability of a pathogen to cause illness in humans that may be exposed either to the feed that was fed to the animals or to the animals themselves.

We look at the severity of illness, the likelihood of exposure, and the ability to mitigate the contaminant across the farm-to-fork continuum. This is an analysis that has been based on commercial foods and feeds and would not necessarily address foods or feeds that are produced on farms, such as silage.

Data from the CVM compliance programs serve as the basis for determination of the public health significance of these particular pathogens which were used for this analysis; and, also, a recent CVM guidance document on the presence of Salmonella in foods and feeds

for animals has assisted in the determination of significance for these particular pathogens.

Now I want to shift to chemical contaminants. As mentioned earlier, we don't have a lot of information on chemical contaminants in foods. There is not an objective database necessarily such as there is with CDC that we could utilize. So assessing the contaminants has been a little more problematic.

Due to the scarcity of data, a task order was issued by FDA for the development of a model that included expert elicitation, that provided a list of chemicals, and provided the weights and the scoring criteria for those chemicals.

Chemicals were divided into five particular bins: allergens, toxic elements, mycotoxins, pesticide residues, and other chemicals, which would include things such as the dioxins, furans, acrylomide, and also abused antibiotics in animal feeds. This was a task order issued to the Institute of Food Technologists. They developed the expert panel that was used. A subcontract was also provided to RTI, who developed and built the model itself.

The criteria of this model address: exposure — that is, the likelihood or level of human or animal exposure to the chemical contaminant in food; health effects — severity of illness or toxicity; and

controllability – that is, can the hazard be controlled in manufacturing, in the environment, or do we have the existence of government policy controls such as guidance documents and regulations.

This model does account for data uncertainty.

Again, I would point out that we did not address approved food additives, so BPA was not addressed. The expert panel populated the chemical list, the criteria weights, and the suggested scores.

The model itself does allow us to separate allergens out, so we can rank the allergens individually versus the other chemicals. Because we recognize fully how important allergens are, we are still in internal discussions about how to move forward with doing this analysis, whether to include allergens separately or to merge them all together.

Again, the rankings were not necessarily that striking in terms of – some of the things you would expect to show up at the top showed up at the top.

Our next steps are, since we have very preliminary results, that we need to have this approach peer-reviewed so that we feel confident that the approach will stand up to scrutiny. We anticipate that some time after some of the current rules that are being addressed through FSMA – that is the PC rule, the produce rule,

FSBP(?), et cetera – that we will again be able to focus our attention to FSMA 104 and FSMA 204. FSMA 204, as Yuhuan will tell you, does require a rule. It requires a regulation. FSMA 104 does not. So anything we produce is strictly in the guidance format.

I anticipate that once the other rules become finalized and are implemented that we will again be able to refocus efforts in this area.

We will engage in further analysis, public meetings, consideration of public comments, and ultimate production of the ranked contaminant lists in draft and final form. It should be pointed out that these rankings provide a basis for overlay of other issues that Erik mentioned previously, where we can look at things like feasibility, cost, and stakeholder input in order to determine rankings that make sense for our issues.

With that, I am going to end it and answer your questions. Thank you very much.

DR. HAYES: Thank you for a nice overview.

Agenda Item: Clarifying Questions

DR. HAYES: It looks to me like we've got a number of lights on, so I assume that means you have questions. We'll start over with you.

DR. RUZANTE: Thanks, Mickey.

Let me see if I understand correctly. You were

using human illness, CDC data, with their attribution from Painter's paper, which is based on outbreak data, to do your ranking for the most significant contaminants?

DR. PARISH: Correct.

DR. RUZANTE: So, obviously, you know all the limitations that there is with that. Is there any sort of plan to look at other ways besides outbreak data to do that?

I think this is also related to the mandate of revising that every 2 years. Is this something you intend to revise every 2 years as far as new data goals, or it's even on the table every 2 years if there is something — a new methodology? You can actually even come up with a totally different framework. I shouldn't say maybe totally different, but if there is room for adjusting methodology as well as data every 2 years?

I have another couple of questions.

DR. PARISH: Sure. Juliana, yes, we do anticipate that this approach will have to be flexible. As I mentioned earlier, we already foresee a couple of obstacles in using the CDC data. So we understand that there are going to be some differences. So we are going to have to devise methods to deal with those differences while trying to maintain as much objectivity as we can.

We do recognize that the database for pathogens

is limited. There are issues with the database. There are tens of thousands of line entries, and yet we cannot utilize many of them because of the fact that they do not identify an etiological agent or they do not identify a food component. So we recognize there are limitations there, yes.

DR. RUZANTE: And then I know this is a task for us, but I was wondering if there was any thought on what is the most significant contaminant, so where your cutoff, in a sense — if you guys had thought about any, because obviously you come up with the ranking.

DR. PARISH: Yes, we thought about it a lot actually. Yes, we thought about it a lot, spent months in discussions on this very thing: What is significant and what does it mean?

One possible method is to simply look at those food/pathogen pairs which account for some percentage of the total financial burden that exists; for example, maybe 90 percent of the financial burden, or perhaps 50 percent of the financial burden.

When we do that, it comes down to five, six, seven of the pathogens in the various food commodities that are — I want to say most significant, but have the greatest impact on public health.

DR. RUZANTE: And the cost being direct medical

costs?

DR. PARISH: Medical plus the loss of qualities. So our economists do monetize the loss of qualities, add that into the medical costs and come up with a cost per illness.

DR. RUZANTE: Finally, you mentioned uncertainty in also some of your model criteria for chemicals. So that means you don't have any of that for the microbiological ones?

DR. PARISH: We have not addressed uncertainty specifically in relation to the microbiological analysis that we've done, recognizing that there certainly is variability that does exist. But we have not specifically addressed uncertainty.

DR. RANGAN: I was a little surprised that Salmonella was not on your list of pathogens, so I would be curious about that.

A related question has to do with antibiotic resistance. A lot of the outbreaks this year, the ongoing one with Foster Farms has all been about seven different multi-drug-resistant Salmonella. So I was wondering if you would speak about Salmonella itself and whether you are considering antibiotic resistance as well in your selection of pathogens.

DR. PARISH: In terms of the pathogens, the

pathogens basically are derived from the CDC database. I apologize if Salmonella was not on the list because it certainly was, yes, and was ranked quite high, as a matter of fact.

DR. RANGAN: Okay. It wasn't on that slide.

DR. PARISH: I apologize. It should have been, yes.

DR. PARISH: Okay, thanks.

I guess one other thing is just recall data would seem to be important as well to look in addition to outbreak data.

DR. PARISH: That actually could be done. We do obviously have a lot of information. We have information from the RFR system, the reportable food system, that we could also look at that addresses a lot of recalls.

DR. RANGAN: And can you speak to antibiotic resistance?

DR. PARISH: Antibiotic resistance. We have not specifically addressed antibiotic resistance in terms of the pathogens per se. In terms of the chemicals, I know that the expert panel did address the abuse of antibiotics in animal feed, so there are antibiotics that show up on the chemical list, the ranked chemical list for animal foods and feeds.

DR. SANTERRE: Mickey, would you say that this

approach really pushes chemical contaminants into the backseat and really favors microbial, which probably should be the case? And is there any consideration of adding economic impact to this model, adding that data to what CDC gives you? Because most of the chemicals will probably show up much more predominantly if we look at economic impact.

DR. PARISH: No, I would not say that we were pushing chemicals to the side, Charlie. We do believe that chemicals are an important part of this whole analysis. I think we started off with the microorganisms because, number one, they are really critical, they are very important. Number two, we did have data, actual hard numbers that could be analyzed, and I really like to get in and come up with standard deviations and plot data and that sort of thing. So that was part.

We had a large group at the very beginning of about 10 to 12 people, as I recall, trying to frame how we're going to move forward on this. So this wasn't just Mickey Parish doing this. I just want to make sure that you understand that.

The chemicals are important. We recognize that there is going to be a certain degree of uncertainty because of the fact that we don't have all the objective data, and the analysis that RTI developed, the model they

developed, does actually give us an uncertainty score. So we have some idea of how much confidence we have in the individual scores that are developed.

I hope that answers your question.

DR. WILLETT: I was also going to raise the same question about antibiotic resistance, because it does seem like it has fallen between the cracks. It is a huge and substantially growing issue. The antibiotic contamination doesn't really address that except very indirectly, and microbial testing it sounds like isn't catching that either.

So was it really discussed adequately to rationally put it off the table, or is this something that we should be encouraging to consider further? I am realizing that you have a lot on your plate already.

DR. PARISH: Well, I think that is a topic that the Food Advisory Committee can certainly bring to the table, and that's one of the reasons we're here, is to say here's the approach we've taken; what's good and what's bad? What have we missed and how can we move forward on this?

I would suggest that we do recognize fully that antibiotic resistance of pathogens is a critical issue. We don't address it per se in our pathogen model that we've developed at this point because it is based strictly on the

CDC data. If there are other overlays that we should be looking at to overlay the ranking that develops that would include antibiotic resistance, then we would like for the committee to provide input.

DR. ARMBRUST: Just one thing I want to try to make sure I've clarified and that the rest of the committee is aware too. The one thing I see with 104 that is going to be extremely important, you've got seven rules that are out for public comment that are still open right now. This is going to be a very critical part to really implementing each one of those particular rules. It's going to be a very big of each one of those. Is that correct?

DR. PARISH: I don't know how critical this activity is to implementing the rules. I do think that this is important and will influence things like our surveillance programs, our compliance programs, resource allocations, and things of that nature.

I am less aware that this is going to specifically push — now, it certainly could in terms of what an inspector might do when they go into a facility that's under the preventive controls rule. It might impact how that inspector views the particular pathogen.

One of the questions we had when it came to most significance is yes, we can rank these things, but oftentimes this is going to be food-based, so that if you

are a manufacturer of a particular product where Salmonella is not a concern, where some of these things that rank very highly really are of little concern to you, but this other organism which perhaps ranked fairly low on the list is your most significant pathogen for you, then we have to be aware of that and our inspectors have to be aware of that as well.

DR. ARMBRUST: The other place where I see this coming into play too is produce, the produce safety rule, where you've really got certain foods, agricultural products, that have been notorious. I am thinking sprouts, for instance, where there have been contamination issues over and over again. This particular process to me would be very important there also.

DR. PARISH: I don't disagree at all. I think it is an important thing. I've been saying for years now that 104 is one of the more important parts of FSMA. Maybe I'm finally getting through a little bit. We'll see.

DR. MEYER: Do you think it is going to be possible to get the same kind of confidence from the chemical data list as a microbial? I don't see how it is as evident from chemical content of food and causality to disease, human disease, unless it's an acute poisoning, as it is with microbials.

DR. PARISH: I fully agree that is a very

important point and a difficult issue to address. We did find that the expert panel, when they met to talk about all of these issues, had that very same question: How do we address the fact that we don't numbers of illnesses per chemical per year in certain foods?

I think that they did a nice job in trying to come up with specific criteria and the weights for the criteria and the scoring that they provided to each weight, to come up with something that's at least a starting point for us.

Again, this is going to be publicly vetted. We're going to have a lot of discussions about this. I don't know exactly when some sort of final document will come out. But you're right, there is less certainty, I believe, with the chemical side than with the microbial.

DR. LINKOV: Could you provide details on the quantitative approaches that they used to prioritize? You mentioned cost-benefit analysis. Is it only a kind of quantitative type of prioritization that you do, or do you have any other logic model, any risk-based approach?

DR. PARISH: I am not an economist, I am not a biostatistician. I will tell you that they do engage in a lot of different analytical approaches. Our economists, I think, are world class, they are excellent. They do an excellent job in trying to address some of these what I

think are highly complicated issues in a way that provides some sort of answer that can come down to some monetary value that helps us to approach this particular instance.

In terms of other types of analyses they do, I am afraid I am the right person to ask, but I can see if there is additional information.

DR. LINKOV: The problem is that in a situation of high uncertainty and lack of statistical foundation for this, monetizing may not be the optimal way to prioritize. Of course, if you have enough information, that's the way to do it, but in a situation like this, it may be too much uncertainty to deal with. So I would appreciate more information.

DR. PARISH: All right.

DR. HAYES: We have time for one more question if the answer can be made within 45 seconds.

DR. RUZANTE: It's a quick question. So, Mickey, the iRISK is not coming into play for this one?

DR. PARISH: We have not addressed iRISK at this point. It is something that we certainly could look at. iRISK could provide some interesting information. We have not addressed it, no.

DR. HAYES: Thank you very much for a well-prepared talk and for your response to the various questions.

Agenda Item: Overview of Current Approach of FSMA Section 204: High Risk Foods Model

DR. HAYES: Dr. Chen is next up. It looks to me like we're getting an upper level. This is a 204 discussion, as opposed to a 104 discussion. So we're moving into a higher level.

DR. CHEN: Good morning, everyone. I actually put this presentation together with Sherri Dennis and Sherri McGarry, who are also here in the audience. Our plan is to give you an overview of the current approach to high-risk food designation for product tracing.

I will begin with the requirements in FSMA for high-risk designation specific to product tracing, to provide the regulatory context; and then talk about FDA's draft approach, including characteristics of the high-risk food risk-ranking model; and then spend some time on data, data needs, and some of the challenges that we've recognized in developing this approach.

We have some ideas about how to approach these, but there are areas that we are still grappling with, so I will share some examples of some of the issues and challenges. At the end, we would be happy to entertain questions that the committee might have on the current approach.

As Mickey mentioned, the requirement for high-

risk food designation is in FSMA Section 204, the provision on enhancing tracking and tracing of food and recordkeeping. The designation of a list of high-risk food is a component, an essential component, of the proposed rulemaking process to establish recordkeeping requirements that are appropriate and necessary for facilities that manufacture, process, pack, or hold high-risk food designated by the Secretary, for obvious reasons, in order to allow us to rapidly and effectively identify these foods and recipients of these foods during an outbreak situation or other events.

Furthermore, in the law itself, Congress actually mandated that high-risk food designation must be based on a number of specific factors, six of them. I would like to go over these factors briefly just to illustrate the bounds that we must consider in developing the approach.

The first factor is the known safety risks of a particular food, including the history and severity of illness outbreaks.

Second, the likelihood that a particular food has a high potential risk for contamination, both microbial and chemical contamination, or would support the growth of pathogens.

Factor 3 is the point in the manufacturing process of the food where contamination is most likely to

occur.

Factor 4, the likelihood of contamination and steps taken during the manufacturing process to reduce contamination.

The fifth factor has to do with consumption, the likelihood that consuming a particular food will result in illness.

Lastly, number 6, the likely or known severity, including health and economic impacts, of a foodborne illness attributed to a particular food.

Given these mandates, our general approach for designating high-risk food includes a number of steps, including developing an approach, gathering information, conducting expert elicitation to address data gaps, and so on.

So far, we have developed an approach based on the FSMA requirements. We have tried to find a way to connect the different factors based on available data and information. Having a predictive approach is inherent in the FSMA mandate in that the FSMA requirements not only include requiring FDA to consider outbreaks and the severity of illness, but really also consider the likelihood of contamination, the characteristics of the food, whether the food supports growth or not, and also very prominently the manufacturing process and steps taken

during manufacturing to control contamination and minimize contamination.

We have developed an approach, and we are in the process of gathering input from various stakeholders on how best to approach the designation. As with the most significant contaminant project, we have also conducted an expert elicitation through a task order to IFT to help us identify some of the data gaps that we've identified.

Then we have also contracted with RTI International to operationalize the approach in a model that allows us to calculate risk scores for a number of food/hazard pairs.

There are other steps as well in this process, so eventually, hopefully, it will lead us to a point where we can designate a list of high-risk foods based on outputs of the model and other considerations.

So we have developed a draft approach document. As part of our process to engage stakeholders, we have issued a Federal Register notice to seek public comments to help us to refine the approach. We invited comments on a few specific issues; for example, whether there are alternative approaches to high-risk food designation; whether additional criteria other than those that are outlined in the approach document — which I will show you some specifics in a minute — whether there should be other

criteria included considering the factors that are mandated by Congress; whether we should assign different weights to different criteria; whether we should make any changes to the scoring system; how should we classify food for the evaluation; how should we select representative foods.

We also took the opportunity to request data and information from stakeholders on the prevalence of contamination, the level of contamination, typical steps and control measures used by industry in the manufacturing process, and information in other areas, such as the health impact of acute or chronic exposures to chemical contaminants and undeclared allergens.

What is in the draft approach? The approach that we've developed accounts for both the characteristics of food and the hazards. It accounts for both human foods and animal foods, as well as their manufacturing process. And, of course, it accounts for both microbial and chemical hazards, including undeclared allergens.

Although FSMA requires that FDA designate a list of high-risk foods, we realize that in order to apply the FSMA factors, it is necessary for us to first take into consideration the characteristics of the foods and known or reasonably foreseeable hazards. In other words, we have to start with food/hazard combinations, food/hazard pairs in the model.

In the end, though, this is not anticipated to be a food/hazard list; rather, it is a food list that we will be designating in the end.

A key consideration in the high-risk food approach is the classification of foods or food categories. Our first step is to identify a comprehensive list of food/hazard pairs representative of all FDA-regulated food products as candidates for scoring in the model.

We wanted to use data that are available to guide us in this effort, so in the draft approach, the classification is based on the scheme that is used in the Reportable Food Registry definitions, which cover most of the FDA-regulated food products and also, to some extent, the IFR definitions considering both the food characteristics and manufacturing processes.

There are 28 RFR categories. There is a category, for example, on low-acid canned food, another category for raw agricultural commodity produce, and then another category for seafood, for example. Within each category, there are example commodities. I will come back to some of these examples later on. Again, our goal is to select representative foods among these RFR categories as a starting point and try to come up with a list of food/hazard pairs as candidates for scoring.

With that as an introduction, what I would like

to do now is to talk a little bit about the characteristics of the high-risk food risk-ranking model.

The draft model is a semi-quantitative model with scoring for seven criteria. We selected this approach, which is the multi-criteria decision analysis approach after an evaluation of the available methods and tools that we have developed at FDA and others have developed and published. We chose this methodology and this approach because we think that it's adaptive to different types of hazards, and it is also flexible to allow us to consider different foods or different food categories. Most importantly, we think that it provides a means for us to consider all the factors mandated in FSMA and find a way to link the factors together in a model to calculate a risk score.

Also, this is a method that we have used in a previous risk-ranking model for produce, which was published a few years ago by Anderson and colleagues. We do have some experience in developing and applying this type of model for produce and pathogens, so we are adopting the Anderson model here and will make changes so that we can account for the FSMA factors.

The seven criteria in the models are: the frequency of outbreaks and occurrence of illness; severity of illness; likelihood of contamination; the potential for

the pathogen to grow and the shelf life of the food. Then we have criteria on the manufacturing process, contamination likelihood, and intervention during that process; consumption; and then economic impacts. Most of these factors pertain to the food/hazard pair. Only criterion 2 is specific to the hazard itself. Criterion 6 is for the consumption of the food.

This figure shows the relationship between the seven criteria in the draft high-risk food model and the six factors required by FSMA. What we have tried to do is to represent each of the FSMA factors by one or more criteria in the high-risk food model.

Once we have the criteria, then the next step is to define the scoring matrix for the seven criteria in the model. I would like to show an example scoring matrix. In this case it is for the criterion on the likelihood of contamination of the hazard in food, criterion 3.

The scoring matrix involves the scores and definition for the different scoring bins. Here we are defining likelihood of contamination for microbial hazard as the detection of the pathogen. For chemical hazard, it’s the detection of a chemical hazard above an action level or above an allowable level.

When we look into the data, when we have quantitative data, then depending on the likelihood of

contamination, the percent contamination rate, then we will assign a score of 1, 3, or 9 to that particular food/hazard pair. If there is no known detection of a pathogen or, in the case of chemical hazard, if there is no known detection of a chemical hazard above an action level, above an allowable level, then we will assign a score of zero.

One of the challenges we recognize is that we don't always have data for all the criteria. Sometimes we don't have data for criterion 3 for some of the food/hazard pairs, so when we don't have quantitative data, what we are thinking is to rely on other indicators; for example, we would look into the number of recalls for that particular food/hazard pair in the FDA database or the number of RFR reports or other indicators. Some of the things that we're looking at right now are whether and how we can use data from some of our compliance sampling, for example.

For each of the seven criteria, we will take the data and the information and group the data and information in the scoring bins and then assign a numerical value. As mentioned, for each of the food/hazard pairs, where there are quantitative data, such as the frequency of outbreaks, number of cases, hospitalization rate, which is an indicator for severity, the prevalence of a hazard in food, then the data would be used in the scoring.

Where data are not available, then we would use

alternatives such as qualitative descriptions and scoring based on subject matter expert opinions.

Once we have the score for the seven criteria, then the calculation of the scoring – the scoring for the food/hazard pair is quite simple. I put a few hypothetical examples here on this slide for different foods, for different hazards, and the pairing. So based on the scores for the individual criteria, let's say if we look at pathogen A, food A, then you will simply sum the score for the seven criteria to calculate the risk score for the food/hazard pair.

In developing the draft approach and in the initial implementation of the approach, we do recognize a number of challenges and issues. I have listed a few of them on this slide. Again, some of these challenges, we've got some ideas about how to approach them, but there are areas where we are still trying to gather more inputs and more information.

For example, what is the level of granularity of food classification that is necessary and supportable by data?

What approaches can we take to combine data and expert opinions in the scoring and ranking of the food/hazard pairs? Expert elicitation is an approach that we've used in the past. It is consistent with what we've

done. We have experience in how to do expert elicitation. The challenge here is because we have to rely on both data and expert opinion, how should we go about combining data and expert opinions in the model, not only scoring of the food/hazard pair then in a subsequent ranking?

Then how should we assign weights to the criterion? Should be assign different weights, and if so, which criteria should receive more weight?

And then how do we aggregate scores for food/hazard pairs? For some of the foods on the candidate list, they have multiple risk scores because they are associated with more than one hazard. So in that situation, how should we aggregate the multiple food/hazard scores to one food score for a food?

These are examples of some of the challenges and issues. I will just provide some more specific examples to illustrate this.

What we see here is an example, a food granularity example. Seafood is one of the 28 RFR categories, and finfish is an example commodity for seafood. The question is, how granular should we identify the representative foods? When we look into the available data and information, for a certain hazard such as Ciguatoxin, not all the specifies in finfish are associated with Ciguatoxin. We actually know which species are

associated with outbreaks due to Ciguatoxin. The same thing for Salmonella contamination and outbreaks of Salmonella, outbreaks that are linked to finfish.

Oh, by the way, if you wonder if oysters is a finfish, it is not. This is just part of a bigger table.

But the question is how granular should the representative food be selected when we identify a food/hazard pair for scoring.

Here's another example. Produce, raw agricultural commodity produce, fresh produce, is an RFR category. Fresh fruits is an example commodity. Within that we know there are tropical fruits. Then the next level is the food and the pathogen that are implicated in outbreaks or involved in recalls. For some of the tropical fruits, actually from experience we know that there could be potential contamination. For example, tropical fruits of different types can be potentially contaminated with Listeria monocytogenes.

Again, with this information, what we need to decide is the level of granularity when we select the representative food. The consideration is that even though we know the specific food/hazard pairs that are implicated in outbreaks or in recalls, once we decide on the food/hazard pair, it affects how we use the data for the other criteria. In some cases the data for the other

criteria may not be as granular as the outbreak data. Say, consumption, we may not have specific consumption data for mango or papaya. We may have more confidence in the consumption data for tropical fruits, for example.

Then what I would like to do next is to talk a little bit about the data and some of the challenges specific to data and some of the approaches and available methodology that we are considering.

Looking at the entire model and all the criteria in the draft risk-ranking model, these are the data needs and some of the data sources that we are aware of. It is very data-intense, really, in order to score each food/hazard pair for all seven criteria.

One thing I would like to note is that we recognize that for some of these criteria industry data would actually be quite helpful to us in terms of the scoring of the likelihood of contamination, the growth potential, shelf life, and in particular control measures available in the industry, the manufacturing process control, and the likelihood-of-contamination data that might be available in data that are collected by industry.

But we are looking at all sources that are available to us in order to obtain data for the scoring. The published literature, of course, government surveys and investigation. We have also commissioned several studies

in the past and we are going to make use of those studies. In the absence of data, we are again relying on expert elicitation to fill some of the data gaps. Lastly, we also use the Federal Register notice as a mechanism to issue a call for data and make use of data that are provided by industry in response to the notice.

In fact we have received quite a bit of data and information in response to the notice that we issued in February. We are in the process of reviewing the data and the information that was submitted.

Just to go back to the criterion on the likelihood of contamination, in this particular example we have conducted a comprehensive literature search as part of the task order to IFT and RTI to look for data specific to food/hazard pairs.

Currently, the likelihood of contamination for the food/hazard pair is determines by the weighted contamination rate based on the number of samples. The weighted percent positive are calculated the same for microbial hazards and chemical hazards based on the definition. Again, where we don’t have quantitative data, then we would rely on other indicators to score this particular criterion.

Earlier today when Paul gave the talk, he mentioned about the TDS data. That is a source of data for

the high-risk food project as well. We use the data from the TDS program to determine the likelihood of contamination for the contaminants that are in there and also on the list of food/hazard candidates for scoring for the high-risk food model.

We know that there are data from our sampling assignments in the compliance program, both the domestic sampling and the import sampling assignments. There is also “for-cause” sampling that would generate data during, for example, sampling that is conducted during an outbreak investigation. Again, what we’re trying to decide is whether there is a way for us to make use of those sampling data from the compliance program, the sampling data from for-cause investigation, as a data source in the high-risk food model.

These are some of the challenges that we recognize in terms of data:

How do we combine data from different studies that have sometimes different designs and have differences in the number of samples, study years, and study location?

How can we incorporate data from the recall database and the RFR report?

Again, as I mentioned, how do we incorporate the compliance sampling data and the for-cause sampling data, because we recognize that these programs are not designed

to specifically determine the baseline likelihood of contamination, not to evaluate industry-level performance.

Again, as I mentioned earlier, how do we combine data and expert opinions?

There is also a data timeliness issue. What time frame do we use? We have data back maybe since the 1990s or since the 2000s up to now. What time frame should we use for the various criteria – outbreak data, contamination? What time frame from our surveillance assignments or different kinds of studies should we use?

And then once we decide on a time frame, let's say, since 1998 – that is the number that we selected in the draft approach document – then how do we deal with the differences in terms of more recent data versus earlier data? In some cases we do have more recent data or we do have evidence that there have been changes in industry practices in certain areas, and we can make an evaluation as to the relevance of the older data. But sometimes we may not have more recent data, and we may not have evidence regarding whether there have been changes in practices.

It is easier when we do have evidence. This is one of the areas where we have information, we actually have survey data to show the differences in contamination rate or the prevalence of a pathogen in certain food products based on survey studies that are conducted a

decade apart.

This particular example is for Listeria monocytogenes contamination in ready-to-eat foods. What we are seeing here is the prevalence in four food categories: smoked seafood, seafood salad, soft ripened and semi-soft cheese, and deli-type salads. This was a study that was reported in 2003 and a more recent study that was conducted by FDA and ARS.

I wanted to note that the recent survey, the 2013 survey, I only show you preliminary data from phase 1. But this is actually part of a larger interagency survey study that involved USDA FSIS.

We look at the data in 2003 and the percent positive or the prevalence from the 2013 survey, and we've done a statistical analysis on the data. Actually, the 2013 prevalence is actually significantly lower for all four categories. So in this case we are able to say we have a survey study, we have more recent data. We can use the more recent data in the scoring. But more generally, though, we don't have this kind of data in all cases.

We need to then deal with the issue of how do we weight contamination data from studies that have different sample size, different dates, and different geographic locations? So far in our preliminary work we only look at the number of samples from different studies. When we

evaluated the comments submitted to the docket, one of the themes in the comments is about the timeliness of the data, basically the study dates.

We went back and looked at some of the methodologies that we've developed over the years in our risk assessment. We were quite glad to find that we actually have a methodology in place to address the data timeliness issue. This is a method that we developed more than 10 years ago when FDA FSIS developed the Listeria in ready-to-eat food risk assessment.

Basically, we would calculate a study weight based on the number of samples, the study date, and the geographic location. More recent studies will receive higher weight, a larger number of samples will receive higher study weights, and a location that is relevant to the food supply in the United States would receive a higher study weight. So that is a methodology that we could use to address the data timeliness issue.

In addition to weighting data, we also need to consider how we weight the different criteria. The draft high-risk food approach, right now we have the same weight for all the criteria. Basically, each of the seven criteria receives a weight of 1. But, clearly, if we were to assign different weights to these different criteria, the risk score for the food/hazard pair will change,

depending on which criteria will receive higher weight and which will receive lower.

Again, there is the aggregating scores issue. I highlighted food B on this table because this would be a situation where one food shows up with multiple risk scores on the list because multiple hazards are associated with this particular food.

In the model we can calculate the scores for the food/hazard pair, say food B/pathogen A, food B/pathogen B, but the question remains, how do we calculate a risk score for food B given that we have these multiple scores right now in the first round of the scoring. So that is one of the issues that we're still looking for inputs on.

Where are we in this overall process for designating high-risk foods? We are kind of in between steps 3 and 4. We've used the FSMA factors to define an approach, define the criteria and the scoring matrix in the approach.

We have developed a comprehensive list of food/hazard pairs as an initial step, a comprehensive list representative of FDA-regulated foods. We are in the process of collecting data for the scoring for these food/hazard pairs and executing the model to determine risk scores for the food/hazard pairs.

We still have a long way to go. As I mentioned,

we are reviewing comments, and we are in the process of refining the draft model.

In closing I would just like to acknowledge our Project Advisory Group. We have a PAG within FDA for the High Risk Food project to help us address various issues.

I would also like to acknowledge the subject matter experts and the expert panel that IFT and RTI put together in assisting us. Thank you.

DR. HAYES: Thank you very much.

Agenda Item: Clarifying Questions

DR. HAYES: We have time for a few questions. I have been told by Karen that I must give you one hour for lunch. I don't know if that's a congressional mandate or an FDA mandate. We have about 7 or 8 minutes for questions. I see a lot of lights to my left and only one to my right, so I will go my right, Charlie.

DR. SANTERRE: I will make it quick.

I would suggest this approach for high-risk chemical foods, or high-risk chemical hazards in food pairs be separated between chronic and acute. It obviously comes out of the microbial world and not the chemical world, but there are going to be 2,000 chemical hazards that we are going to find in our foods where we don't have any tolerances or action limits for any illness data. Putting those two together, in my book, just doesn't make sense.

They almost have to be separated between things that cause acute effects which are measurable with illnesses and hospital events and things that could cause cancer in 50-60 years.

DR. SHREFFLER: Wally, can I just, really super briefly, just add my voice to that recommendation? It is certainly very pertinent for allergens as well in that category, where you do have the opportunity to get some of that data.

DR. MCBURNEY: This is to be more for reporting than monitoring, correct? Because it's not a live model of looking at microbiological risk where you start to have a report from one region and then you realize that it's covering a greater and greater percentage of the country. So clarity on — I mean is this sort of a year-end looking back on how we've done, or is this a real-time assessment that we have a high-risk event in progress?

DR. CHEN: It is an assessment based on the data from the past.

DR. MCBURNEY: From the past, okay.

Then in your weighting criteria, it's cumulative. Have you ever thought of — or is there the possibility that a criterion that has a zero renders the whole score to zero?

DR. CHEN: Yes. For example, in the criteria for

growth for a food/hazard pair involving chemicals, the score will be zero because we know chemicals do not multiply in food. So it depends on the characteristic of the food and the characteristic of the hazard.

DR. MCBURNEY: But your examples all totaled — there wasn't a zero that went to a zero because it was a cumulative —

DR. CHEN: Yes. The zero is criteria-specific. So if it turns out that all seven criteria individually receive a zero, then the total score for the food/hazard pair would be zero.

DR. WALLACE: Three brief statements, if I may. Nice presentation. If we stay on this slide, just for the record, I would like to state that I believe that each of the criteria are weighted unequally. They should be weighted unequally rather than all receive the same weight. I think that's a pretty obvious statement.

Also, if you go back to slide 28, please, along that weighting discussion is that this suggested formula for adjusting the weight, I believe each of those factors should receive differences in weight. I think that sample size, geographic weight, and the weight of the date of the study should not be weighted equally in adjusting the weighting of the criteria in the next slide.

DR. CHEN: Can you be more specific?

DR. WALLACE: More recent data may carry much more weight than having a lot of data that is 10 years old. That's what I'm saying.

DR. CHEN: Yes.

DR. WALLACE: So each of those factors on the right-hand side of that equation should have a weighting factor. They should not be equal. That's my opinion.

If you go back to slide 29, please, the last thing is I think we all realize there's a great deal of uncertainty in the final score here, and I think that that should be included in the communication of whatever this score is, there should be some sort of indication of confidence or variability, range, uncertainty, or whatever. Not just report a single number, because if you report it like this, 22 looks to be bigger than 21. I doubt that there is any difference there when you look at the uncertainties.

DR. CHEN: Yes, and in the model that we've developed, like what Mickey was mentioning about the most significant food contaminants, there is also an attempt to evaluate the uncertainty range for these scores.

DR. WALLACE: Absolutely. Thank you.

DR. RUZANTE: Two questions, a quick one and one more philosophical, I guess.

For the severity, you are not including long-term

sequelae(?) for the microbe list. Just a clarification. Can you remember?

DR. CHEN: We do actually because recently, looking at the requirements in FSMA for both microbial and chemical, and there was no exclusion for chronic chemical, so in the severity, in our definition for the scoring matrix, where there is the hospitalization rate, mortality rate, that's easier, like the Scallan paper. Where there is no quantitative, there is a qualitative description about the severity. It involves the chronic impact in the definition itself.

But we are looking to further refine that qualitative definition. The long-term effect also would be reflected in the calculation of criteria 7, the economic impact, which is a health-related economic impact. It is calculated based on the cost per illness. The cost per illness takes into account the quality, medical cost, and some element of chronic effect is considered, but we can do better.

DR. RUZANTE: Now my question or comment, I am not quite sure how to put it. But you mentioned the challenge of how to weight criteria if there is need for any other criterion to be part of it. That is also part of our task. So I guess this question, comment, whatever, is not just for you but also for FDA leadership, because it's

our task also to say how to weight criteria and what criteria should be used.

I am sort of conflicted a little bit because when I think about criteria for decision making, I think about a decision maker coming up with those criteria, not necessarily — I think a group like this could validate or suggest consideration of other criteria — and I am conflicted about that, trying to think about — I could see both ways, really, that the criteria that you are going to consider could come from a group like this. But to me it almost makes sense that decision makers — the ones making the decisions about what they need to do next — are the ones coming up. The weights, the same way.

Or if you were to decide to say, okay, this needs to be more of an outside process as well, then I wonder — then you probably need a more representative group of stakeholders.

But I am just a little interested in how FDA intends to use this information. I guess my understanding was that decision makers are the ones say what matters to us is cost, consumer perception, public health risk. Public health risk is our priority, so the weight there is going to be X, and so on and so forth.

I am just a little confused about how putting it in the Federal Register and having folks saying, oh, you

should weight like this or like that, and you're missing this criterion or that criterion. I am just a little — how the process of actually incorporating that into your final methodology, how that — it is, as I said, more of a philosophical question rather than a very —

DR. HAYES: We will hold it as a comment because it is now 11:45. We have to be back at 12:45. So that gives us the mandated one hour for lunch, and you will tell us how to get there. We have to be escorted to the cafeteria. Be back at 12:45, please. Thank you very much.

(Recess for lunch)

A F T E R N O O N S E S S I O N (12:47 p.m.)

DR. HAYES: We are going to resume after our mandated 1-hour lunch period, which has now extended to 1 hour plus 1 minute. We are going to our next presentation, and Heather Tate is going to talk to us about the role of some acronym in risk assessment.

Agenda Item: The Role of NARMS in Risk Analysis

DR. TATE: I am going to be talking about NARMS' role in risk analysis. NARMS stands for the National Antimicrobial Resistance Monitoring System. Why does FDA have an antimicrobial resistance monitoring system? To answer that question, let's start with the use of antimicrobials in animal agriculture.

Antimicrobials are used in veterinary medicine to treat diseased animals, control outbreaks of disease in a herd or group, and also to prevent infections. Antimicrobials have, until recently, also been used to increase feed efficiency and promote weight gain in food animals. Many have referred to this practice as growth promotion. This has proven to be the most controversial use of antimicrobials in animal agriculture, and this practice is discouraged by FDA as it poses an unnecessary risk for the development of resistance in foodborne bacteria. Therefore, in 2013, as noted here, FDA issued new guidance for industry to begin phasing out growth

promotion uses of veterinary antimicrobials.

In its efforts to assess what the risks of antimicrobial use in animal agriculture are, the Center looks for answers to these two questions. How does the use of antimicrobials in food animal production affect resistance among foodborne pathogens and commensals, and also, what is the impact on public health?

The CVM strategy to answer those questions is aimed at assessing relationships between antimicrobial use in agriculture and potential human health consequences and involves a multi-pronged approach that includes the following elements: expanded research activities, revised safety assessment process, which was our Guidance for Industry 152, and that was issued in 2003. Also, we revised judicious use guidance, which was Guidance for Industry 209 which came out in 2012, and then Guidance for Industry 2013, which I just spoke about, guiding industry to phase out production uses.

We also are updating the veterinary feed directive. We have enhanced surveillance activities, which is NARMS, and that began in 1996. We also have education and outreach activities and we participate in international activities regarding antimicrobial use in agriculture.

This talk is going to focus on NARMS.

NARMS is an interagency collaboration between

FDA, CDC and USDA, and the goals are to monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats and animals; to disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria; to conduct research to better understand the emergence, persistence and spread of antimicrobial resistance; and also to assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals. On this last point, I'd like to point out that NARMS not only has a pre-approval function, but it also serves as a post-approval monitoring system.

In brief, here is how the NARMS data collection tool is designed. This talk will essentially answer these questions: What is sampled? For NARMS, we sample food animals, retail meats and humans. Where are the samples collected? We collect them at slaughter, at retail, and public health laboratories collect fecal samples from humans. What are the geographic areas? We have nationwide sampling for the food animal and human component of NARMS, and then the retail component is in select states, as well as one of the bacteria in humans component, and I'll get to that a little later.

How many samples are collected? It varies per source. For food animals and humans, we have a

statistically robust sampling design. For the retail meats, not so much. What are the samples analyzed for? They're all analyzed for resistant enteric bacteria. Some of the considerations we have are cost, representativeness of the sample, new technologies, et cetera. I realize that a number of surveillance programs discussed today may have used a risk-ranking method to prioritize appropriate resources, and I just wanted to note that NARMS does not use a risk-ranking tool *per se* to answer any of these questions; however, we do make informed decisions based on a number of factors such as what are other countries doing, because we want to globally harmonize our methods.

What does WHO and OIE, which is the veterinary equivalent of WHO, recommend for an integrated surveillance antimicrobial resistance monitoring program? What existing resources do we already have, which is a big factor. Also, what drugs are important for monitoring. Here, risk-ranking is used, and I'll go into detail on that more in my future slides.

NARMS follows a design that is recommended by the WHO Advisory Group for Integrated Surveillance of Antimicrobial Resistance, or WHO AGISAR. The study population encompasses humans, food-producing animals and retail meats. The microorganisms that we target include major foodborne pathogens and sentinel organisms, which

I'll go into detail about in the next slide. And we consider these following elements in our sampling design including sample source, sample information, sampling representativeness, collection frequency and sample size. We also consider a number of elements for lab testing methodology including culture methods, susceptibility testing methods and isolate storage.

The NARMS study populations are selected to evaluate resistance trends across the food production and supply chain. As stated in the previous slide, NARMS monitors resistant bacteria in food-producing animals, retail meats and humans. You can also see here which of the agencies are responsible for each of the arms of NARMS. USDA oversees the collection and testing of isolates from food-producing animals. FDA oversees the retail aspect of the program, and CDC of course looks at the human aspect.

You will also see the start dates for each of the arms of the program. The first arm was started with the human sampling in 1996 with CDC. Then USDA followed with food-producing animal sampling in 1997, and FDA came onboard with retail sampling in 2002.

Here are the target organisms that each of the arms surveys. We are all culturing samples for Campylobacter and non-typhoidal Salmonella. These microorganisms were selected because they are major

foodborne pathogens in the U.S. And Enterococcus and generic or non-serotyped E. coli are also monitored by both USDA and FDA. Enterococcus and E. coli were selected as sentinel organisms because they are common and numerous, and they are used to monitor antimicrobial selection pressures among gram positive and gram negative organisms, respectively.

The other organisms listed here that CDC monitors are selected to guide therapy in humans.

And finally, NARMS does conduct periodic pilot studies to assess resistance among other organisms that might be found in food -- I've listed MRSA, C.diff and VRE. These pilot study organisms are selected according to changing epidemiology of disease and also research interests.

This is the same slide but visualized in a slightly different way. The NARMS program collects samples across the farm-to-fork continuum to assess resistance in bacteria from food animals, resistance in bacteria that consumers may potentially be exposed to through consumption of retail meats, and resistance in bacteria from people who would have presumably become sickened through consumption of contaminated meat. I say presumably because people can become sick with these bacteria through non-meat and even non-foodborne sources.

I'll now talk a little about the details of the sampling design of each of the arms. For human and food sources of bacteria, accommodating possible biases associated with sample source is relatively straightforward. However, there are many potential sampling points for food animals. If we collect samples from animals on farm, it is the most direct indication of resistance arising from antimicrobial use on farm; however, those samples may not reflect the pathogens that are recovered post-slaughter that people are eventually exposed to. If we collect samples from the holding pens that animals are placed in before they go to slaughter, it may be a better reflection of what is expected to contaminate retail meats; however, they are less indicative of antimicrobial use on farm.

In the end, we chose the post-slaughter sampling because it is the most convenient and affordable point to collect animal samples. Convenience and affordability are obviously two big considerations for us. Also, samples collected here may overlap with samples collected at the retail and farm points.

We have also been evaluating the feasibility of an on-farm sampling program through a few pilot studies conducted in partnership with USDA and universities, but I won't go into detail about those in this talk.

Here is more information about the NARMS animal-sampling component. USDA monitors bacteria from swine, cattle, chicken and turkeys, and these animals were selected because they receive a majority of the antimicrobials that CVM regulates. They are also associated with a majority of meat-borne infections.

Prior to 2013, we relied exclusively on HACCP samples which, from 2006 through 2011, were collected through a risk-based sampling system, and that is illustrated in the top half of the slide. Because samples were risk-based, we do not know how representative these samples were of total food production. But beginning in January 2013, the NARMS food-animal component now collects cecal samples, shown in the bottom half of the slide, as opposed to the previously collected carcass swabs and rensaids that were collected through HACCP.

Cecal samples are collected pre-chill and they're exposed to less plant contamination and they are more indicative of resistance as a result of drug use on the farm. Furthermore, all the plants are subject to cecal sampling, so this is a nationally representative sampling system. In 2013, USDA collected almost 5,000 cecal samples. I want to note, however, that the susceptibility testing that is illustrated in the top half of the slide does continue through FSIS's HACCP Salmonella verification

program, so we do continue to monitor results from that program.

The retail meat surveillance is outlined here. States that participate in the retail meat surveillance program are selected based on existing public health infrastructure. We now have 14 states, but initially we started with 10 states, and those 10 states came from FoodNet. FoodNet is CDC's Foodborne Diseases Active Surveillance Network. Of course, we've grown now to 14 states. The other four NARMS retail meat states are not part of FoodNet.

Each state lab purchases 10 packages each of chicken breasts, pork chops, ground turkey and ground beef for a month, and these meat cuts are selected based on what is consumed and available nationwide. For instance, we found that turkey legs are not available in many places but ground turkey is. Meat cuts are also selected based on the appropriate matrices for isolation of bacteria. We do include chicken with bone in, skin on, and that is collected because Campylobacter adhere more to chicken with skin on than they do to the actual chicken meat.

The number of meat packages is based on what was recommended in a pilot study that was conducted in one state, Iowa, over a 1-year period. Although we've expanded the program to several states, we continue to use that

number of 40 meats per month collected at each site.

All of the 14 sites culture for Salmonella and Campylobacter, and only four of the sites culture for the sentinel organisms E. coli and Enterococcus. The total retail meat samples we collect are approximately 6,700 meats per year, and those isolates are sent to FDA Center for Veterinary Medicine for susceptibility testing and other testing which includes Pulsed Field Gel Electrophoresis and whole genome sequencing, so we are a part of PulseNet and we do collaborate with other FDA centers and other agencies for whole genome sequencing methodologies.

More isolates are needed for statistically strong trend analysis. We've done the power calculations and we understand how many samples we need to say that a certain amount of change in resistance in any given year is significant, and it's a lot more than we currently collect. One of our limitations right now is funding to purchase and test more meat packages, but our desire is to sample in major metropolitan areas which I've shown here with the yellow dots -- areas like Dallas, Texas. In California, we're predominantly sampling from the San Francisco area right now but we would like to also collect samples in L.A., Chicago, Boston, Miami and New York City.

This is how sampling locations are determined. A

state public health laboratory will select the zip codes from which it is feasible to sample, and these are zip code areas in California. The zip codes are typically situated near the state public health laboratory. They give the zip codes to FDA, and we use what's called a chain store guide to identify grocery store locations within the sample areas. FDA and CDC then randomly select 10 grocery stores to sample from each month and we give these lists to the state for the year.

The list of 10 grocery stores is actually broken out into five primary stores and five secondary stores to sample from each month. The designated purchaser in any particular state then visits the five primary stores to collect two packages each of the retail commodities, and to ensure that we're getting two unique samples, we ask that they select two different establishment numbers or sell-by dates or lot numbers. Finally, if the meats are not found at the primary store, the sample goes to the secondary store.

Now I'm going to talk about human isolate sampling. Fecal samples that have been collected by health practitioners end up at the state laboratory where they're cultured for isolates, and the isolates are sent to CDC for susceptibility testing and additional testing.

Each target organism undergoes a different

sampling strategy, and for non-typhoidal Salmonella, the sample strategy has evolved since NARMS inception. In 1996, 14 sites were submitting Salmonella samples. Now, 53 sites, including the 50 state laboratories and three local health departments, submit Salmonella to CDC. They're submitting every 20th isolate. Approximately 2,000 isolates are submitted to CDC each year.

For Campylobacter surveillance, only the 10 FoodNet sites, which are highlighted in green, submit Campylobacter isolates to CDC. The number of Campylobacter isolates submitted to CDC is dependent upon the burden of illness in that state. Briefly, all agencies use a broth microdilution method, and we follow both internal and external quality assurance programs to ensure that methods and results are harmonized across all arms.

The antimicrobials on the NARMS microbroth dilution panel are selected based on their importance in treating human and veterinary infections, and also they are selected as epidemiological markers. Some drugs are ranked critically important. Some are highly important, and some are just important. The importance rankings illustrated here are for drugs on the gram negative or Salmonella and E. coli panel and the Campylobacter microbroth dilution panel.

Importance rankings are assessed through various

criteria which I will describe in a later slide. These particular rankings shown here are from FDA's Guidance for Industry 152, Appendix A, but there are others that NARMS collectively looks to including WHO and OIE. There's actually quite a bit of overlap between the rankings from each of these institutions.

My last set of slides is going to focus on how NARMS data are used for risk analysis. CVM employs a qualitative risk analysis to determine the safety and efficacy of veterinary antimicrobials. It is described in detail in our Guidance for Industry 152.

The components of the risk analysis are shown here. The hazard has been defined as human illness, in this case, caused by an antimicrobial-resistant bacteria attributable to an animal-derived food commodity and treated with the human antimicrobial drug of interest. The release assessment estimates the probability that the proposed use of the antimicrobial new animal drug in food-producing animals will result in the emergence or selection of a resistant bacteria in an animal.

The exposure assessment describes the likelihood of human exposure to foodborne bacteria of human health concern through animal-derived food products. I want to note that for purposes of this qualitative risk assessment, FDA assumes that the probability that bacteria in or on the

animal at slaughter may be used as an estimate of the probability of human exposure to that bacterial species in that food commodity derived from that animal.

The consequence assessment describes the relationship between specified exposures to a biological agent and the consequences of those exposures. For purposes of this risk assessment, FDA has decided that the potential human health consequences of exposure to a defined hazardous agent may be estimated qualitatively by considering the human medical importance of the antimicrobial drug in question.

All of these factors, including the hazard characterization, combine to create the overall estimation of risk of a particular veterinary antimicrobial.

So NARMS actually informs the release assessment and the exposure assessment, which I'll talk about in the next slide. There are several release parameters within the release assessment which risk analysts at CVM try to get information about. NARMS surveillance data are used to describe the spectrum of activity of a particular drug, and NARMS research, which I briefly mentioned in the slide on NARMS' goals, can also be used to answer questions about resistance mechanisms, resistance transfer and selection pressure. These other parameters obviously come from other sources.

For the exposure assessment, this chart shows the possible process for ranking qualitatively the probability of human exposure to a given bacteria in a given food commodity. NARMS data are used, in addition to other data, to assess the probability of food contamination. The amount of food consumed comes from the USDA Economic Research Service data and other sources. According to this chart, if the amount of ground turkey consumed is high and the amount of ground turkey contaminated with Salmonella is high, then the probability of a person being exposed to Salmonella by consuming ground turkey is also high.

Again, the consequence assessment is the probability that human exposure to a resistant bacteria results in an adverse health outcome, and CVM says that health outcome can be estimated by the medical importance of a particular drug. So here are some examples of the medical importance of various antimicrobials.

CVM outlines its qualitative risk ranking tool in Appendix A of Guidance for Industry 152. Five criteria are used to rank whether a drug is critically important, highly important, or just important, and there's obviously some weighting in this criteria. Criteria 1 and 2 are more important than 3, 4 and 5.

The overall risk estimation represents the potential for human health to be adversely impacted by the

selection or emergence of antimicrobial-resistant foodborne bacteria associated with the use of the drug in food-producing animals. Here are some possible risk estimation outcomes for various release exposure and consequence assessment categories.

These are the examples of possible risk-mitigation strategies based on the level of risk. For instance, if a veterinary antimicrobial were considered to be of high risk to human health, then CVM might market it as a prescription drug only with extra-label use restriction or short-time use, and the drug would be subject to post-approval monitoring through NARMS and also advisory committee review.

Thank you for listening to the talk, and I hope that you consider some of the elements that I went through in your discussions today and tomorrow.

Agenda Item: Clarifying Questions

DR. HAYES: Thank you very much. We're open for questions.

DR. RANGAN: I just want to say that I think NARMS is a really important program in terms of interagency working together. We have done a lot of communication with NARMS and with all of the agencies, and I think it's a great model as we're thinking about how we develop a comprehensive risk-assessment program. You guys have done

a great job, so I just want to commend you for that.

I have a couple of questions. One is regarding USDA testing. Just to be clear, the on-farm stuff really just started recently, so most of that data that's in NARMS right now is from the plant itself. I think there are advantages to plant in that so many farms go into a plant, and if cross-contamination is happening there, then that's really important to capture. So I think both of those, on-farm and at the plant, are really important points.

I'm curious about Campylobacter testing. It's an important pathogen. USDA started testing for it in poultry in 2009. Just recently, they, for lack of a better term, at least we feel like they've dumbed-down their Campylobacter testing so it's frankly less sensitive, and they've moved to what they used to have as a combined qualitative and quantitative program that you might be familiar with for testing. They have now narrowed that to just quantitative, which I know scientifically sounds like that's the right one but it turns out that's far less sensitive than the qualitative one.

What is FDA using for Campylobacter testing? Did you make the change USDA made, or are you still using the qualitative and quantitative assessments for Campylobacter?

DR. TATE: I can't speak in detail about this because I'm not fully aware of the microbiology methods

that are used, but I do know FDA has not changed its method at all. I know that we've had conversations with USDA about the combination -- or how to combine the results from those two methods, because I think there were some years of overlap in use of the qualitative and quantitative methods. So, how to combine those when we're looking at analysis of trends over time.

DR. RUZANTE: You mentioned the other areas that you would like to sample, and you also mentioned you are far below having a sample size number that you actually would be able to have more confidence in your trends. How far from the ideal, or how far is NARMS from becoming a more representative surveillance program where you could have more of a national picture as well as with enough power to actually speak to some of the trends? Is it far from that point?

DR. TATE: It all depends on funding. Right now, we are quite a distance. We had recommended that for poultry samples alone, each year we should collect something on the order of 9,000 and we're not collecting anywhere near that many. A lot of it has to do with funding.

We're also looking at how to ensure that the samples we do collect in each of the states are very representative of what people are exposed to within that

state. A lot of the zip codes that are chosen are chosen as a matter of convenience, what is closest to the state health department. Some states have looked into trying to sample in more distant regions of their state and see if that makes any difference in what they see in terms of bacterial isolate recovery and resistance, and also what that means in terms of the types of brands that are offered and things of that nature.

Yes, there are two pieces there -- expanding the number of samples and, hence, the number of isolates that we are able to capture in NARMS, and then also looking to see whether the samples we are collecting are representative of what the majority of people in the U.S. are exposed to.

DR. SANTERRE: How are you addressing antibiotic cocktails? If I'm a producer and I know I've got to get my animals to slaughter with a certain level of a certain antibiotic, I might put in two or three other antibiotics to stay below the tolerances for those, and thereby accelerate this microbial resistance by using a cocktail. Are you looking at cocktails? How are you addressing that?

DR. TATE: We are not really looking at use right now. That's one of the steps that we're going to start looking at as now this Guidance for Industry 213 has come out. One of the things we said we were going to do in

terms of monitoring the success of Guidance 213 is to look at use of drugs in the animal population.

We have not been able to capture accurately single-drug use versus cocktails, but we do know that is an issue; we do understand that these cocktails might be spurring co-resistance. For instance, a cocktail that doesn't contain tetracycline might incite tetracycline resistance in bacteria recovered from food animals. That's something that we understand would be an issue, but trying to reconcile that with the resistance data that we have without use data is kind of difficult.

DR. SANTERRE: One thing that might help is CVM has been working with FSIS to develop, to accept performance-based analytical methods. When they test a carcass for certain antibiotics they can use as many as eight to 15 different assays to find one violative carcass. This movement toward multi-residue methods where you can test for a whole barrage of drugs in a single analysis is much more efficient and can really get you better data relative to the cocktails in the future. I would recommend really pushing for the performance-based analytical methods in testing of carcasses.

DR. WILLETT: This was an informative presentation. I was not aware of what NARMS is doing, and it's clear that you do need more samples to have good

statistical power.

Can you say anything about what you've learned so far, given your limited testing?

DR. TATE: What we have learned so far is information that CVM has been able to use for some of the policies that have come out recently. With regard to cephalosporin resistance, we did see an increase in cephalosporin resistance among all of the arms that we were sampling -- the food animal arm and the retail and human. Particularly in the serovar heidelberg we saw an increase in resistance. In 2012, CVM put out an extra label use order prohibition for cephalosporin in food animals, so we continue to monitor the trends in cephalosporin resistance to see if that has had any effect.

We also, in the nineties when fluoroquinolone was first introduced to human medicine, started to monitor resistance among fluoroquinolones in humans. Then, when it was under consideration as a new drug in animals, we started to incorporate animal monitoring, and we found that there was actually a really great risk analysis done by I think Voss and Bartholomew and colleagues, showing that resistance in chickens had the potential to create resistant Campylobacter in humans -- fluoroquinolone-resistant Campylobacter in humans.

In 2005, the application for fluoroquinolone use

in poultry was withdrawn, so we've continued to monitor fluoroquinolone resistance in animals and humans and retail meats since then, and, unfortunately, we have not seen any significant drop in resistance among Campylobacter from animals. There are other researchers out there who have shown that fluoroquinolone-resistant Campylobacter are more hardy in (?) fluoroquinolone-susceptible Campylobacter, so that might explain why. But that's something else we continue to monitor.

I think those are the two major ones I can cite.

DR. McBURNEY: This is a really important program and I appreciate your insights. I have a question that's a combination of strategy and perception. You've shown nice maps where you've got coverage in all of the states, but actually, if you look at our meat, often our poultry comes through very different strategies or different forms, whether it's local to market or it's high-production facilities. Have you looked at thinking of mapping it as percentage of facilities that are being tested rather than coverage of states?

DR. TATE: In the animal arm, we are looking at percent of facilities, in terms of the cecal sampling, the percent of facilities that are monitored. I don't know the details about that. USDA has done a great job of developing that program. I am aware that all facilities

are subject to sampling under the new cecal sampling method.

For the retail portion, we don't really know too much about the distribution of food products, so we're trying to capture that data right now, working with the states to understand the whole universe of brands that are available in which particular states. To use Foster Farms as an example, we know it's widely distributed on the West Coast in California and Oregon. If, let's say for instance, Foster Farms was the major poultry brand in Texas, then do we even need to try and collect samples from Dallas, as I had indicated earlier.

Those are some questions that we're trying to answer with participation from the state labs.

DR. LINKOV: The presentation really provided a good foundation for prioritization. The only issue I see is a little bit methodologically it needs to be enhanced. This is like bringing risk assessment and multi-criteria decision analysis together, and there are many nuances that need to be thought through. For example, how to rate criteria, and then the issue of integration. For example, in a sense you're using (?) modeling and it seems like if exposure is high but consequences are low you say it is still high, but in reality, if you don't have consequences, high exposure means nothing. So this multiplicity versus

(?) needs to be thought through in the process of developing measures here.

The other important issue -- actually what you do is not risk analysis. What you do is basically risk-based decision-making. All that makes sense only in the prioritization context. You're not getting absolute measures of risk associated with each agent here. But I guess that may be the subject of more detailed discussions.

DR. HAYES: Thank you very much for an excellent presentation.

Our next presentation is Dr. Bennett, and she is going to tell us about the National Residue Program.

Agenda Item: National Residue Program

DR. BENNETT: Good afternoon. My name is Patty Bennett and I work at the Food Safety and Inspection Service and one of my primary responsibilities is to help manage the National Residue Program. The point of my presentation is simply as a warm-up to Dr. LaBarre, who will actually go over one of the proposals we have of kind of re-thinking how we consider chemical hazards and to prioritize them.

But I thought that since this is for FDA, it might be helpful to start out and explain very briefly what the National Residue Program is about and how it has evolved and some of the significant changes that we've made

over the last few years, because hopefully that will help to lay the groundwork for when Dr. LaBarre talks.

I think one of the most important things I can tell you is that of all the sampling programs we have within FSIS, this is one that is truly an interagency project or cooperative effort. We work very closely with our partners in FDA, EPA, and other agencies. We work with CDC and APHIS and AMS. Again, primarily, I have several FDA and EPA counterparts who are on speed dial depending on whatever happens to be brewing this particular week.

We operate under a Memorandum of Understanding that has been in place since 1984 and we are in the process of updating it. In general, it says what most of our MOUs say, that we agree to work cooperatively together, and I believe that is very true in the years that I've been with this program. From the MOU have come our IRCGs, so again, an interagency work group at a very technical level, at my level, as well as a surveillance advisory team which, while also technical, involves many more people and more of an annual meeting where we discuss how we see the National Residue Program over the next year and sometimes over the next several years.

Prior to 2012, our program looked pretty much like this, and I'm using Bob veal as one production class for an example. FSIS, of course, has jurisdiction over

several different production classes. This is one of our primary production classes, not only in terms of volume produced but in terms of chemical residue issues.

The way this worked prior to 2012 was we would collect on average about 300 samples, and we would look for a particular chemical or particular chemical class using generally just one method. Under antibiotics, we would collect close to 300 samples and we would just be looking for antibiotics, and then the 300 or 253 samples just for Flunixin, and obviously we didn't get close to 300 samples in the last one, just for the group of Sulfas that were in the method that we were looking at. I say this because even though this was the program we had in place and it was the best we were doing at the time, that was the only thing we were looking for in any given sample, so we really had no idea what else the animal might have been exposed to. These were the only things that we were going to test for in these samples.

You can see here that we took a little under 700 samples in this production class looking for just these three different types of -- and actually, in this case, there are only veterinary drugs. The total chemicals looked at were about 60, but again, not for each sample taken. Again, drawing across the board, in the middle column for Flunixin, when we only collected the 253 samples

we only looked for one chemical.

In 2012, we took what I think is a phenomenal step forward and, as an agency -- of course we made this decision in the year past but it actually came into fruition in July of 2012 -- we made the decision to introduce many multi-analytic methods into the National Residue Program, and really that has become our framework for moving forward and to move away from the single analyte methods. They're just not very efficient and they only give us a small bit of information.

In addition to implementing multi-analytic methods, the other huge significant change we made was that we were now going to take one sample and with that one sample we were going to test as many methods as we could against that one sample. So here's the same slaughter class or production class in 2014, and you can see there are seven methods in the first column that we are testing against one sample that would come through as a Bob veal. Again, on the far right, each of those samples we tested, 182 chemicals, which to me is so fantastic. I am a veterinarian and I understand that taking these measures really gives us a much more holistic look at what this animal was exposed to, not only in terms of veterinary drugs which we're always concerned about, especially in this particular slaughter class, but other things such as

pesticides and even metals.

To look at a larger picture, this is our scheduled sampling program across the major production classes for fiscal year 2014, which is just about to end. Again, you can see all of the primary production classes over which we have oversight and all the different methods we use when collecting the samples.

That leads us to where we are right now. Again, this program is about 47 years old, and our focus has been almost exclusively in that period of time on veterinary drugs and pesticides. I'm certainly not saying that those aren't important because they are very important both to FSIS and certainly to FDA and EPA, but I think we all understand that our world is much bigger than veterinary drugs and pesticides and there are other chemical hazards of which we should be aware. So the question for us becomes how we develop an intelligence framework that we can use to get this information.

Up until this point, even though technically we have a program where we make a determination of which chemicals we want to test for in our program, the reality is that it's very difficult for us to get the information to feed these models that we've been using, and primarily we have relied on expert elicitation. What does FDA want us to test this year? What new chemical have they just

registered for use in dairy cows, or what formulation have they changed -- we talked about cephalosporins a few minutes ago -- that we maybe need to focus on. Or EPA has a list of pesticides that they're very interested in because of the assessments they do in their work.

We think we can be a little more systematic about what we're doing. Not to say that expert elicitation isn't important, but again, as has been talked about before, we only have so many resources that we can devote to this program and we really want the most bang for our buck.

The other thing we realize in FSIS is that there's always an opportunity cost to what we do with this program. The more resources we devote to this program, perhaps there are less resources devoted to other sampling programs that we have in the agency and it always becomes where do we want to put our energy and what is going to be the most important thing that will provide the most public health emphasis.

In addition to thinking about what are the chemical hazards that we should be considering, again, outside of veterinary drugs and pesticides, how do we prioritize them? How do we make that list, and what should that look like? And the follow-up question would just be simply how do we manage this program. Knowing that we can't test for everything, possibly we can't test for

everything in every production class, and possibly we could test for chemicals for a period of time, but at what point do we say we probably have enough information that we no longer need to expend the energy to continue to test for this chemical. And which chemicals do we need to test for political reasons; which chemicals are really about public health; which chemicals are even canaries in our coal mine? Maybe it's not so much for public health but they give us a good indicator when something else is out of whack.

Our methods primarily test for the chemicals that we tell the methods to test for. What about scanning for the unknowns? How many resources should we put into just looking at our samples and looking for spikes and trying to run those down? Do we have the energy to do that? Is that important enough that we should be looking for the next melamine because we're not expecting it? What happens when it happens, and how quickly will it take us to find it, and how are we going to afford all that and manage it and put it into practice and wrap policies around it?

That's where we are right now with our program. I'm really excited. I think there's a lot of momentum around looking into the future and realizing that our world is very big and we're going to do the very best job that we can. I realize there are a lot of us who have talked about the different sampling programs, so we're very excited to

see what kind of recommendations come out of this committee, and hopefully we can take some of them home and wrap them up and run back to our senior management and say, yes, but the committee told us we should be doing this.

If you have any questions, I'm happy to answer them and then I'll turn it over to Dr. LaBarre.

DR. HAYES: Questions? I don’t see any red lights going on anywhere so we'll let you sit down. But don't leave. They may have questions for you after the next presentation.

Agenda Item: Logic Model

DR. LA BARRE: Hi. My name is David LaBarre. I don't have a number one slide that tells you who I am and what the title is but I'm going to be talking about latent risk models. The Logic model is actually a subset of those types of models. I'll explain what that is in a minute.

This first slide talks about the general attributes of the model, but first we probably should consider what we might use the model for. It's obvious from what Patty said that we'd want to use it for risk ranking of chemical residues for public health risk. That would be an obvious thing. But it has been suggested that we also might use it for ranking economic risk, domestic or international, and I can show you an example of that later on.

This type of model probably would be useful for ranking a number of different types of chemical residues. It could be antibiotics and pesticides and environmental contaminants. What I'm going to show you is a general model, an example of a demonstration model just to get you familiar with the concept of how these models are developed.

I guess the most important application would be for our laboratories when they have a small number of chemicals, maybe 10 or 20 chemicals or residues, and they're thinking about developing a standardized method for the tissues that we analyze, which would be muscle, kidney and liver, and that is actually a very lengthy process that they have to devote time and money to. They might want to know which chemical they want to do first, so that would probably be the most critical application.

I'm going to describe a latent public health risk model that could be used for determining chemical hazard risk to the public and chemical hazard prioritization. This is a simple linear risk model characterizing only one risk factor. When I say risk factor, we're talking about essentially a non-linear model that we linearized by using the Logit transformation. So when I say linear, it's actually non-linear modeling and we've transformed the data so it can be linear.

This is something akin to factor analysis from the social sciences where they would have a number of variables and they would want to extract a factor that's latent in the data. Typically, they will want to extract more than one factor here. I'm going to first describe how we would extract one latent risk factor, but it's possible to extract more than one depending on the type of risk factors.

With these kinds of models we have only partial data from which we estimate the latent risk, for which we have no data. This is the idea of the factor model. In the factor analysis model, we have a dependent variable which is the factor that they want to extract. Here it would be our latent risk, which we have no data for, and for the factor model they have no data. In the factor model they would have the dependent variable which would be a continuous distribution. Then they would have the independent variables on the other side -- the linear equation, which also would be continuous.

However, the type of model I'm describing here that we're using is something quite different. It has a probability distribution for the dependent variable, and then it has categorical distributions for the independent variables. It's very easy to apply different types of data and standardize them and be able to put them on a

commensurate scale, which is very important. So we can have continuous data that's very quantitative and very precise in the model, and then we can have data that's more categorical, more quasi-data that we're not so sure of, and we can put all these types of data in the model.

We're not really restricted to how many levels we can have, either. We can have groups of risk factors. In the case I'm going to show you, on a Likert scale which would be five categorical levels, and then we can have binary -- do we find it in our products or not. Any type of scale. And we can sub-set these, so it's very flexible.

Because we used a specialized algorithm called the expectation maximization or EM algorithm, we can have even 50 percent of the data missing and still make valid estimates of chemical risks, which is another very attractive point of the model. Like I said, we use a probability distribution for the dependent variable on the left side of the equation, and categorical variables on the right side, the linear model.

On the very bottom, we're talking about the linear model so it has intercept and it would have a slope. We can use all sorts of combinations. The model I'm going to describe here, where we have all the slopes equal to 1, actually they fall out of the model and we're only dealing with the intercepts, which is a simplification. But in one

of the models I'll show you later on, if we include more parameters we can extract a whole lot more, but sometimes that's something we may not want to do.

Slide Two – the probability of distribution for the dependent variable is cumulative logistic or equivalently the cumulative normal distribution, which is taken from the Logit or the probit distribution depending on which -- actually, they can be made equivalent by a common factor, so they're essentially the same.

The independent chemical attributes each have their categories described in terms of similar probability distributions that are locally independent. In the model I'm going to describe, we're using logistic transformation of both independent and dependent variables and we're transforming back to have cumulative distributions for the logistics distribution. Like I said, we could use a normal distribution if we wanted.

The model is unique in that we did not alter the model; we chose to fit the data. We have a model that we want the data to correspond to, and if it doesn't really fit the model, then we'll try something more complicated. This is sort of the reverse of the way statisticians usually do it. They'll modify the model in order to fit the data, and here we are not doing that.

This is high school math. Y equals m X + b. Y

is the dependent variable, m is the slope, X is the independent and b is the intercept. As I said before, we're dealing with Y as the probability distribution and X is actually a categorical distribution. So the model we're talking about -- if you're familiar with logistic transformation for binary data where you have live-dead counts of animals that you expose to a toxin or whatever, then that would be a binary model. But here in this case we're talking about a 5-point Likert scale, so that would be five levels.

With the binary model, we're talking about the log odds ratio, which is just the probability divided by 1 minus the probability and we'll take the logarithm of that where you only have two levels that you're looking at.

Here, we're talking about five levels, so what we do is, if we have five levels, and we actually only have four equations, we're dealing with one risk factor. That's just because of the way we solve simultaneous linear equations. So we take a basic base level and divide that into the next level up, the probability. So the Logit (P_{ji}/P_{ji-1}), that's something we have to find from the data. We don't have that, first of all, so, like I said, the EM algorithm gives us an iterative process to estimate this Logit of (P_{ji}/P_{ji-1}), and then estimate the four levels that will back-transform into the five levels.

So we estimate for each of the risk factors, four Logits -- we have four intercepts, we have slopes all equal to one, and X_j is each of the chemicals. What we're trying to do is find the distribution across all the chemicals for these five categories.

There are five probability levels. Here's what we have for the independent variables. We're looking at five different curves that correspond to the levels 1 through 5. They've been back-transformed from our model that we could solve. This is what I mean, that we're seeing if the data actually fit this, and we have a number of statistical parameters we can look at or statistical tests we can do to determine if this model actually fits. What I'm showing you is a model that does fit -- the data does fit the model. This is what we have for each of the risk factors. Here, one of the risk factors is MRL. In the model I'm going to show you we have 29, but this is just a demonstration.

Here are the 29 on the left. You can see we have one for MRL, cancer, tolerance, ADI, Rfd, NOEL, LOEL, blah, blah. These are just examples. Where we have 27, 28, 29, FISI, FDA-EPA and Consumer, these would be opinion levels that could be binary or whatever we want to make them. If we can get stakeholder opinion, that could also be put into the model. So it's very flexible what we can do with this.

What I don't have is for a particular chemical if it's found in FEED, yes or no. If we have levels of that we could put that in. Also, we collect for residues at FSIS; we collect data from three tissues -- kidney, liver and muscle. Primarily we would be interested in the muscle but we would also probably have data from those other tissues, too. What we look at with residues is, is it present, yes or no. That would be one risk factor. Is it violative, yes or no? If it is violative, yes or no? So there would be three factors we could put in for each of the tissues, and I sort of left that out of these 29 variables.

This is in comparison to the EPA prioritization criteria for the TSCA work plan chemicals. They only have four risk levels. The model is applicable to that. You have to realize if we have more risk factors, then we can actually look at more chemicals that we can distinguish between. The fewer risk factors we have, the harder to distinguish.

Here's one method for looking at the statistical attributes. We have 29 chemical attributes to evaluate. This is taken from a Winsteps model that is a very simple type model that I'm using to describe this light and variable model, like a risk model.

What we have are 29 different size circles and

they correspond to -- if they're large, that means we are less certain; if they're smaller, we are more certain, but these are all pretty much the same size. We're looking on the vertical axis of risk; the highest risk is at 2, the lowest risk is at minus-2. That's how we evaluate these risk factors.

If we go on the horizontal axis, we're looking at the actual data fit. If there is underfit, that means there's more randomness in the data and we are less sure about it and we probably have fewer data points present and we have a lot of missing data. On the right and over to the left, it means just the opposite. This is just a way of looking at the data. This is the chemical residue attributes and we can look at the chemical residues themselves.

And the same thing here, highest risk is towards 3, lowest risk minus-5, and the very small circles indicate they are pretty accurate. If we're going less than 4 to minus-4, or actually 2 to minus-2, there's quite a bit of scatter in the data, so we would actually look at the statistical properties of each of these chemicals and evaluate with the risk factors to see why they're out that far. Like I said, usually it's because of missing data.

So there you have 312 chemicals and this is the model I'm focusing on right now.

We take the 312 chemicals and we put them in a diagram like this, and it's a way of plotting risk. So zero, zero, and one of the axes is crossed, zero, zero, point -- that's where we say if they're lower than zero or to the left of zero, we're not so much worried about those. But the ones that in the upper right quadrant, those are the ones we're considering have the most risk. The red ellipsis is indicating those.

Of the 312 chemicals, 83 of those are of EPA concern. I'm sorry I didn't color these, but there are 14 in the ellipsis group that are in the EPA group, so we can rank those, and the others would be chemicals that we would be interested in the prioritization of those. And the ones at the very top of the ellipsis are probably the ones of highest concern but are not on the EPA list. So that's just a way of looking at the data.

This is like a factor model where they'd be looking at more than one factor they're extracting from the data.

Here is a model where we had those 29 risk factors, then we have 10 additional economic factors. So we have a three-dimensional plot where theta-1 on the bottom axis is actually the public health risk and theta-2 is actually the economic risk, and it's about 10 percent of the variance. And the peaks correspond to the risk factors

that are important in the model. So this is just a way of looking at the data for a more complex model.

The simpler models I do in Winsteps are the two-dimensional models where we're extracting one risk factor or risk, public health risk. For these more complex ones, we're trying to extract multiple factors of risk use various packages.

General rules for the datasets -- this is describing a flat file and I'll show you an example in a minute. We're more concerned about the input of the raw data and then how we have to transform that data into the ranks. That's sort of the hard part of this model, going from the raw data which is a variable quality into the ranking. Then, how do we make them commensurate. That's a problem. You can think of an Excel file where the rows are the unique chemicals and the columns would be the common risk factors. So we have that raw data table.

Then we have a second table that we link to the raw data table that has the transformation, the ranks of each of the risk factors. Then we have a third table which holds all the links to the first table, where that data came from. That's probably the most important take home from this -- that we have to document this stuff exhaustively. These types of models are always questionable until they are fully vetted by all the

stakeholders. Otherwise, it's very hard to say it's a valid model.

On the left, we have the 29 risk factors and on the right are the EPA's. So we're going to extract the rows. Here we have a breakdown; that's not the whole matrix of 31. On the left we want to have a matrix that's 312 rows and on the right we'd have 29 columns for the risk factors. The chemical names are on the right. We have descriptive names where the data came from, and that would be linked into the specific files and we would need a link for each of the 29 risk factors. It's very comprehensive what we're trying to do. You can see there's a lot of missing data; this is not a complete file yet.

Here on this slide, we have the 29 risk factors and a block of that big matrix, 12 by 29 matrix. Now we've filled in most of the data but we have still a lot of holes in it. That would be the raw data file that we're using. What we do is put an asterisk for everything that is not present. So this is actually the first table that has all the raw data. This is what we're going to transform. Some of the variables are already in a category. Like the cancer variables, they would be typically taken from National Cancer Institute scaling where they would have one, 2A, 2B, 3, 4, 5. To get a 5-point scale we'd just take the 2A, 2B and put it into category 2.

So we take that and transform everything into the 5-point scale. Here we've got 27 chemicals by 29, so that's only part of the table.

Now, how do we do the coding? We know the maximum and minimum of what we have. If we have raw data that's in quantitative form, say, then we find the maximum and minimum, we find the medium, and then we try to fit a uniform distribution to it. We also calculate how many values are present, how many are missing, and then how many total there are. So we know pretty much about that risk factor, what problems there may be with it.

Then we can plot it out. What this shows -- we can't really fit a uniform distribution because, like on the MRL, one is a lot higher than the rest of them, and on the cancer it's the opposite. That's how we get the weighting of the risk factors, according to how many counts we get across all the chemicals for each of the risk factors. It's the same thing for every risk factor; we want to get the scale commensurate.

So here's a compressed text file that we use for the simplest models. When I say compressed, we have 37 chemicals here, then we have the names on the very right, then we have the compressed -- actually we have here 11 risk factors; it's a very simple model. We have all the levels in there, so number one, chloramphenicol, we have 5-

1-1, et cetera. So there are eleven 5-point scales for what was found for that particular risk factor for that particular chemical. We go down like that, so this would be a typical file, a compressed file.

Now we have some EPA data, raw data, and then we might take it into this Excel flat file. Here we've got the chemical name that we want to rank, and we have where we go with it. We would have one of these for each of the risk factors.

Here's a compressed file that we used for the very simple Winsteps facet software, and we would use like an Excel flat file for the R inputs. On the left is the compressed data. Notice that we have asterisks for missing data, so this is how we do it. Same way in the Excel files. It depends on the program if we can use asterisks or whatever to map out the missing data.

On the right, we have the control file where we have all the risk factor names, and then what the actual 5-point scale levels are. They can be high, medium, low, unknown, whatever. That's another point.

This is the flat file we use for input into an R package. On the second column, we have categories -- pesticide, environmental, veterinary drug - three categories. We can put this into a model. I'm sorry I don't have a graphic for it, but it would be where we do

sub-categories of this latent factor model, so it would have three sub-categories that we could do simultaneously. That's a little more complicated.

Here would be a typical linked file into the raw data file where we have a lot of different kinds of data. We have the actual documents from which the data came, and within the document we have links into the raw data file.

Agenda Item: Clarifying Questions

DR. HAYES: David, can we stop here? I think we've got a very pressing question.

DR. LINKOV: You showed a couple slides ago that you had very little data available for this table, and miraculously it got filled with all kinds of data. How did you do that?

DR. LA BARRE: Here, in this control file, we do the same thing with the R data. It's how we set up the categories, what we are calling those five levels. One of the levels we would have no data for, and that would be the asterisk -- not really the asterisk. An asterisk means no data at all; that would be a 5. But if we have information that says this chemical does not cause cancer absolutely, that would be a 5. And the 1 would be the other way, it always causes cancer.

Then it's how do we define the categories in between, and that's sort of critical. It has to be uniform

across the variables on the 5-point scale. And the 2-point scale has to have the same meaning of those categories across those sub risk factors.

Does that sort of answer your question?

DR. LINKOV: What do you do if you don't have data? You put 2 or 3?

DR. LA BARRE: We put asterisks.

DR. LINKOV: But in that next table.

DR. LA BARRE: Okay. We've got a lot of asterisks in here, maybe 40 percent of the data there is missing.

DR. LINKOV: I think there was another table that showed the kind of link to this one.

DR. LA BARRE: I think what may be confusing is these are different tables that don't represent the same dataset. I'm just trying to be very generic and not be too precise about this. I hope you understand.

If we want to do subsetting of the supporting data that's linked to our raw data file, then we can have a subset that, say, we got from EToxNet data, and here would be an example 2-4-D. So we would have the citation and then within it we would link to individual properties. Here we have physical properties, then we have exposure guidelines, the ADI, the MCI, the RFD and all these things that we might put in the model. So this is how we would

link it into the primary.

Farther down we have maximum residue limits for 2-4-D, and then we'd be taking out for meat and poultry. That's all we'd be interested in for FSIS. For FDA we'd be interested in a whole lot of other things, too. So here would be the file for the EToxNet, a subset.

There's one thing I went over and didn't talk about. This is something that is important for statisticians. We can do this sort of risk factor analysis by using a multiple regression model, but in that type of model there are a couple of characteristics that make it totally inapplicable. On the bottom we have latent risk equals -- a slope trend. Risk 1, Risk 2, blah, blah. What we try to do is estimate those slope factors, A-1 through A-n, but we need data for the latent risk. So we can actually get that if we want. One way of doing that is to take the first principal component of all the risk factors, and if we did that we would have something we could actually use as the risk data, the dependent variable, and we could find the A-1 through A-n.

However, we can't really do that because one thing that makes this latent risk model that we're using, we're using the AM algorithm, is that we can have all the risk factors highly correlated to our latent risk variable that we create from the data, and if we have that in a

multiple linear regression model, that would mean we couldn't really solve it because then we'd have linear dependencies all over the place. We can calculate a variance-co-variance matrix, but when we try to invert it the whole thing blows up.

So that's one thing that's very attractive about this kind of model. We select our risk factors to be highly correlated with our latent risk factors. So, in the process of estimation, a two-step estimation, and maximization steps, we produce a risk factor with very high correlation with all those risk factors. That's probably the take-home message from that. I thought maybe statisticians would be interested in that.

That's all I really have to say. If you have any questions, I'd be glad to answer them.

DR. WALLACE: David, thank you for the presentation. I think I have a general concept of what the logic model is that is being used.

The very last line, as I read it, once again strikes me that you're weighing each risk equally -- each risk factor equally.

DR. LA BARRE: Yes. And that's dependent on if we're using the same -- here we are using a 5-point scale for all the risk factors, so that means we're weighting them equally. However, that doesn't mean, when we develop

that scale, that that is how it originally was. As I showed you, in the distribution of each risk factor, we can actually change the actual weight in how we define those risk categories of the risk factor. By making them larger or smaller, we can have more --

DR. WALLACE: Explain to me, David, where you bring in -- when you do the linear transformation for each risk factor has its own weight method that you use --

DR. LA BARRE: Right. Actually, it's simultaneous.

DR. WALLACE: How do you bring that into the final score for the latent risk, when you have different forms of linear transformation?

DR. LA BARRE: OK. The thing is that they're all the same. This Logit equation -- for each of the categories we have an equation. If we have five categories across all the risk factors, then we have four equations that we're trying to solve. However, that's unique to each risk factor. This would be actually a sum over 29 X's, so it's actually a little bit complicated. The X's are all on commensurate scale, but we use some intuitive magic in order to get the scaling of those risk categories to be where we think they should be.

Like I showed you before, we have MRL where they're weighted at the right side, and we have the cancer

where they are more weighted at the left side. In this case, 1 is the lowest risk and 5 is the highest risk, so that means here is the weighting. This MRL is weighted more for the highest risk level, and the cancer is weighted more for the lowest risk level. By changing the distributions, each of the risk factors, we can alter the weighting.

This is actually a lot simpler than more complicated models, and there are a lot of models where they try to estimate or they'll try to input a weighting factor into their model. What I'm trying to do is develop the simplest model that we could possibly use, and that could be evaluated and talked about and actually approved by the stakeholders. A lot of these models, we don't know where a lot of the variables are coming from -- sometimes it's just mystical. We want to be very precise in where the data comes from and how we create the risk factor category levels and how we derive them. We want to be very transparent. This is actually a transparent model.

DR. WALLACE: And I appreciate that. A quick follow-up, and perhaps you have indicated it but I missed it, and that is where do you get your data from. Is it peer-reviewed sources?

DR. LA BARRE: Preferably from peer-reviewed sources, but we could put good data, we could even put

trash data in the model if we wanted but we're not going to do that. Like I said, we can have highly precise qualitative data and then we can have data that's quantitative versus qualitative, and we could put them all in the model but we'd have to be very careful how we scale it. Actually, what we're doing is highly precise quantitative data, we're actually dumbing down to a median level between the lowest quality and highest quality data.

Then we have to decide on a statistical basis which risk factors we actually want in the model. I'm not going through all that because it's a little bit statistical and not really that interesting for most people, but we have ways of evaluating the risk factors. Like the Winsteps and the other software, they produce hundreds and hundreds of statistics; it's unbelievable. There are over 50 graphs that they produce. You just press a button and it takes a week or two to figure out what's going on.

Like I said, we're trying to fit the model to the data rather than change the model fit. It's sort of a weird way of thinking about modeling but it's actually probably the simplest. I really didn't describe the R models. Essentially, the difference between them is just putting in the numbers for slope factors, where you can have a different slope for every risk factor, and we could

have different intercepts and all sorts of things we can put in there and we could get those two-dimensional or three-dimensional more complicated models quite easily. They're very similar to the Logit model.

DR. LINKOV: I cannot say that I followed all the presentation, but my general impression is that these types of models work when you have a lot of information and primarily based your data on technical information.

I think in this case, in one of the slides the table was like 40 percent empty, and another table before it was only 20 percent filled. I think with this statistical model, you have problems because you have no control over how it gets done. For example, you cannot separate the judgment coming into play, where data come into play, and that's part of the difficulties with this type of model even though you say it's transparent. In a sense, what it doesn't say it's a black box.

I guess that's kind of my take on this. The previous presentation basically used decision analytical models. Those are more manageable, from my point of view. But these type of models, of course --

DR. LA BARRE: Ideally, we would want no missing data or maybe less than 5 or 10 percent of the data missing. What this EM algorithm does is maximizes the expectation for each of the risk factors, essentially, and

also simultaneously maximizes the expectation for the logistic distribution of the overall risk. It's doing a lot of things simultaneously and in generally two steps, but there are a lot of sub-steps involved.

What I'm saying is that the parameters it estimates are usually the same parameter estimates -- they're in the ballpark, let's say, of if you have 40 percent missing data or 50 percent or 60 percent, as you decrease the amount of missing data, then because you're maximizing the expectation, you're actually coming to about the same parameter estimates. That's what is good about this model.

Obviously they are not the same, but they're in the same ballpark and they would very likely -- from the various types of datasets I've used -- very likely they would produce the same ranking. We're not really interested in the precise estimate of risk; we're interested in the ranking. Is this chemical more risky than the next chemical.

We can tell if we've got too much missing data because then we won't be able to separate groups of similar chemicals, similar pesticides. Then we know what we have to do is decrease the number of chemicals in the model or get more data.

DR. LINKOV: Let me ask you this. To run this

model you probably need some technical data, some judgment data from stakeholders, so what would you ask stakeholders? What type of data comes in that model from stakeholders?

DR. LA BARRE: This type of model actually comes from surveys. This is a commonly used model for survey data where you would have maybe five levels, multiple levels of response to a given question or a yes/no or yes/no/maybe. It really best handles the data that is more qualitative, more judgmental. What I've suggested here is it's very easy to put that sort of data in with the more qualitative and more precise data.

DR. RUZANTE: I know FSIS is very good at posting their methods and approaches, guidelines, whatever on the website. I wonder if this is already, if you have that explanation of your approach --

DR. LA BARRE: Not yet. It's coming. The hold-up is that this was a dataset of 312 chemicals. I have it expanded to about 950. The thing is this model, if we expand the number of risk factors out to 50, which is very easy to do because of what I said about the residue data that we collect, then we could get way over 1,000, between 1,000 and 2,000. But that's really not so important, how many chemicals we can assess. We can say, okay, this group of chemicals is more risky than that, but we're more interested in the smaller groups. How we would rank a

group of 10 or 20. So that's more the take home for this type of model.

But like I said, it has been used for surveys and for qualitative data extensively. If you're familiar with SAT, MCATs and all those, this is how they evaluate them, with this type of model.

DR. RUZANTE: And a clarification -- Pat, I think this question is for you. When you change analytical methods, when I read it in the Federal Register it said that the number of samples went down. But it seems like from your presentation it went from 600 to 800, so it seems it went up. I was just a little confused with that.

DR. BENNETT: Actually, prior to 2012, we would collect about 20,000 samples across all of the production classes. But again, if you're collecting 20,000 at 300 a pop, we would only be looking at maybe one method.

DR. RUZANTE: Would they represent -- when you say a sample, would that be an animal? Would a sample be an animal?

DR. BENNETT: Yes, exactly. An inspector gets a task that says you need to go and collect one Bob veal carcass, some liver, some muscle, some kidney, and send it to the lab. So now what we're doing since 2012 is instead of collecting across all production classes, we've focused on most of the volume that we produce in the United States,

and that really is represented by nine major production classes. So we're not really doing the emus right now or the rabbits. But we could.

Instead of taking -- maybe we take 1,000, or 600 for that Bob veal, the standard sampling set right now is 800 samples per production class. But again, where it starts to multiply is that each sample is analyzed using multiple methods and so that's where we get it. We went from 20,000 samples for the program to about 6,400, 6,500 samples, but we're getting many more analyses *in toto* and, also, per sample. Does that make sense?

DR. RUZANTE: But then some animal categories you are not sampling -- you mentioned emus and rabbits -- and they end up not being --

DR. BENNETT: Not necessarily on an annual basis. That comes back to risk. We slaughter 100 million pigs in the United States, and you go, oh my God, how much meat is that -- versus 500,000 rabbits at two pounds a pop.

So what we'd like to do with the scheduled sampling program is this annual surveillance of how are we doing, but we have other sampling programs within the National Residue Program where we can go ahead and target. We say you know what, we haven't done emus for a while; we need to touch base and make sure they're doing okay, so we're going to throw them into the mix this year. But

maybe instead of testing them every year, we're going to use those resources and focus on something else and we'll test them every few years.

DR. RUZANTE: So, a Bob veal, for example, in that case of that animal category, the samples did increase.

DR. BENNETT: Actually, the total number collected probably decreased because we would collect -- say we decide that for every production class, and this is prior to 2012, we were going to use four different methods on four different sets of 300. So 300 times four, that's more like 1200 samples collected for Bob veal. Now, the standard sample number is 800, but instead of just looking at four different methods, maybe we've got the seven or the eight or whatever we have in the queue right now. Again, the 300 samples just got one method versus, now, the 800 samples get seven methods.

For me, it's less about the numbers but it's more about the framework for what we're doing, the things that David is talking about -- do we want to focus on environmental contaminants and do we need to start rolling them into our pesticide methods or bring in another method.

We have a metals method -- which should we be focusing on. Which are the heavy metals that we need to be concerned about.? What energy do we put into surveying for

the unknown? Can we use David's model as a means to help us kind of prioritize.

One of the things I loved -- before, we've always talked about individual chemicals. Here's a bunch of pesticides, here's a bunch of antibiotics. But you noticed in one of the later slides, he was binning them. That's another thing -- if we look at vet drugs as a bin, or pesticides as a bin and environmental contaminants as a bin, are all those bins equal? So we say I'm going to devote so much of the resources for each of the bins, and then within the bins we rank. Or does each of the bins have a different ranking because of what you already know about chemical hazards?

DR. LA BARRE: What Patty is talking about is something I really didn't talk about. Here we have a latent variable model, we're talking about latent risk, generalized risk, but then we can do what's called latent class analysis, and that's exactly what Patty was talking about where we have classes of chemicals. And then we can prioritize the classes and the chemicals within the classes. So that's another type of model that is very easy to do with these types of data input that I described.

Also, as a final parting comment, in the last 10 to 14 years, this particular latent variable analysis has been very popular and pushed forward by the psychiatrists

and psychologists. It's their favorite method of analysis now. Most of their literature uses this model which deals mostly with qualitative data but there is some quantitative data, too.

Also, one thing I've found in just reviewing the literature is there are probably less than 10 examples of government regulatory use of this kind of model, so it's very sparse but hopefully it will become more popular.

DR. WILLETT: The model algorithm has been used for decades epidemiologically and does seem to be an appropriate method to use for this. The biggest uncertainty is usually that, when you're looking at the health risk itself, that comes from toxicological studies and other kinds of data and this usually involves extrapolations across orders of magnitude down to the doses, the levels of exposure that are seen here. It's the best we can do; there's a lot of uncertainty.

But as I understand it, you're really just using this not for saying there's an absolute health risk, but for decision analysis in terms of what to focus resources on.

DR. LA BARRE: Yes, that's the intention; just to use it to rank chemicals and then make a decision.

DR. WILLETT: I think if the interpretation is careful, then that makes a lot of sense.

DR. MEYER: I just want to try to restate that in my words so I understand what you're trying to do. You're using a multi-variant latent analysis type program?

DR. LA BARRE: You could call it that but it's not really -- when you say multivariate, then you're talking about where you have known correlation structure and all that, and you're not dealing with multi co-linearity *per se*. This model loves it. You get the best estimates the more co-linearity you have with the risk factors, and with a multivariate model you just can't --

DR. MEYER: For each of the endpoints -- you had cancer as an example and you had 1 through 5. Those are categorical assignments to just what you think that chemical --

DR. LA BARRE: For that particular variable, risk factor, we used I think the NIH categorization which I said was 1 through 5, but 2A, 2B, so we just collapsed 2A and 2B into --

DR. MEYER: As far as the weighting then, the weighting falls out of the model, doesn't it, as far as those alpha factors? Am I understanding that correctly?

DR. LA BARRE: The weighting is in the definition of the categories, the risk categories, and we try to balance across all the risk factors. We try to come up with a uniform distribution, but some of the risk factors

don't allow us to do that. They'll have a bias on one end or the other. So that's how we actually are weighting, according to what the data is actually telling us.

DR. MEYER: So once you run it all through then, what tells you that cancer is a more informative endpoint, for example, than endocrine disruption?

DR. LA BARRE: What we can do is -- one of the statistics we calculate is the correlation with the latent risk factor that we derive from the data. That's practically how we determine if it's a valuable risk factor or not, by the significance of that correlation. It's sort of a standard analysis.

DR. MEYER: Okay. It is empirically derived from data that you're pulling from past databases.

DR. LA BARRE: The beauty of this which statisticians would love is the fact that we're using a normal distribution, so it's very easy to do these calculations. It's nothing really weird. The logistic distribution is just off by a constant, essentially, so it's just more convenient.

DR. LINKOV: I would like to reiterate that this approach perfectly worked in the example you gave (?) when everything is filled you have a lot of data gaps and you're not even talking about uncertainty; you're talking about missing data, which is the case for chemical

prioritization. It's very difficult to see how that can work because you have all these risk factors that are kind of linear and usually risk factors are grouped or structured in a different way and there are many assumptions here that are not reasonable.

DR. LA BARRE: What I didn’t show you because it's horrendous is how they break the data down. We can look at something like principal components, how much of the variance can be ascribed to each of the risk factors. There are plots and statistics that are derived that tell us if we should throw them out, if there's too much missing data, essentially.

I didn't go into the statistical analysis which is actually quite extensive and propping up our assumptions that we can use this amount of missing data and still make a valid prediction for the coefficients in the model.

I didn't do that. It's very complicated.

DR. LINKOV: But this is part of the problem in my mind and I've been in risk analysis for 20 years.

DR. LA BARRE: We actually calculate the uncertainty of the model with uncertainty analysis We do sensitivity analysis; we do all these things and then we make our decision can we use this model for this data.

DR. LINKOV: It may work, but statistics works only when you have data. And the fundamental problem is

that often in risk analysis we just ignore data because we don't have enough of it, and then we operate with what we have and the danger is that you may be ignoring something that drives the risk because you don't have data. And I --

DR. LA BARRE: That is why we label data that we have -- if there's no data, then we just put an asterisk there and say we don't know and just let the model make its best estimate. Then obviously what we would want to do is collect more data if possible and see what improvement there might be in decreasing the uncertainty.

DR. SANTERRE: It seems like as you try to validate this model, it might be more useful taking something like heavy metals where we have a good set of data as opposed to, say, the melamine and some other emerging contaminants where we don't have much data. Can you comment on that?

DR. LA BARRE: Yes. I agree with you, Charlie, that where we have a lot of data that we're pretty certain is good data, then that would be the best application, for heavy metals especially. Yes, I agree with that evaluation.

DR. HAYES: Thank you very much. I think people are now beginning to process all of the long presentations we've had this morning. I want to thank the various people from FDA who gave presentations. They were clear, concise

and very, very helpful.

Now I guess it falls to us over the next hours that we have this afternoon and tomorrow to respond to the charges and questions. If you'll look in your folder you'll see a little document entitled "Food Advisory Committee Meeting - Charge and Questions." If I have evaluated this correctly, there are three broad question areas, two on the first page falling onto the back, and then one on the second page.

Attached to this is an Appendix which basically gives us a synopsis of the various presentations that we've heard this morning.

My suggestion is that we take a short 5-minute break, reassemble ourselves and begin to at least complete this afternoon the top question laid out for us: Designing and implementing data; a data collection, example areas to be addressed include -- and then there are some questions that we need to respond to.

So if we could take a short break, then we'll return and go to work.

(Break)

Agenda Item: Committee Discussion

DR. HAYES: While we are waiting for everyone to come back, Kendall pointed out to me that the primary questions are on the back of the page, and there is a lot

of redundancy in the first part. So what I was thinking is we might quickly go through both sections on the front and then we can focus most of our attention on the five questions on the second page.

My understanding is that through the course of this, we're being recorded and we've got a transcriber, but Karen is going to be taking down any recommendations that we make, so we're pretty much open to comments and thoughts. Is everybody okay with the way we've set out how we're going to move forward?

DR. RUZANTE: How does the work? Is there a report produced in the end and it comes back to us for revisions and edits? How does that work?

MS. STRAMBLER: Each person gives a recommendation and then you all come together to give a consensus and that is what I'll type up if everybody agrees with it, and that's what I'll put on here.

DR. HAYES: What we'll try to do with the five questions that are on the second page is, in the end, come up with a consensus. This is only my second meeting so I'm no expert, but we did have one where we struggled to come to consensus and we finally did reach consensus at the end of the meeting.

If we can come to a consensus, that's going to be the best way to do this. Hopefully we'll be able to do it

as we move through this.

DR. WALLACE: Mr. Chair, I would entertain the possibility that if there is a very strongly held minority opinion, that that would be recorded as well as --

DR. HAYES: Definitely. If there is a minority opinion, it will be recorded, there's no doubt about that. The goal is to come up with a consensus, but if we don't come up with a consensus and there's a minority opinion, that certainly will be included.

All right. On the first page, just to run through this, the first one says, what food or food products should be sampled. Is this something that we need to add? It seemed to me that they were pretty broad in what they were doing, what foods and food products. Do you think they missed anything that we really ought to point out to them?

DR. WILLETT: Yes. I raised it a little bit earlier, but it does trouble me a little bit. Everything that has been covered, the contaminants, both chemical and microbial, are extremely important and this must be done. Still, if we're looking at the overall healthfulness of the food supply, we're looking at factors that probably are having very modest impacts and missing out on what is really having a much bigger impact, like sodium level, trans-fat level, sugar level.

I would like to have that part of the picture not lost completely. It probably would fit best within the total diet survey, to monitor those variables as well, which would be actually easy to do since they're collecting the samples already. Those are standard assays, not complicated.

In general, there's a parallel between what CDC is doing and what FDA is doing for microbial contamination and chemical contamination, but that isn't existing for sodium and trans-fat and sugar in the same way. In other words, CDC is looking at what they're picking up in human samples and human surveys, but FDA is not doing the parallel work at what's in food.

DR. HAYES: So we could simply make that recommendation, that in addition to what they're doing, it would be worthwhile adding sodium, trans-fat and sugar to whatever analyses they're doing on these food products. Does that kind of catch what you're saying?

DR. WILLETT: Right, yes, in that food survey. Part of the reason is to put into context some of the small levels of contaminants that might be there when people are sort of digging down for the trees and missing the forest -- so often that's what I see happening.

DR. McBURNEY: I think there is validity and we need that, Walt, but I don't think this is the program to

be trying to put that into.

DR. WILLETT: Well, the reason -- don't want to start out *do novo* because in the total food survey you've already spent vast resources in gathering the samples and collecting them. You wouldn't want to go collect other samples to do it.

DR. HAYES: I guess another question I would ask -- meat, for instance. Would you look for sugars there? Or are you more in process foods where you're thinking about the sugars and salts and trans-fats?

DR. WILLETT: You I think would have a plan for being selective just as you are selective for microbial contaminants and other --

DR. HAYES: What I'd like for you to do is put down no more than a paragraph on exactly why you think this ought to be done and how it should be done, and then we can bring it back up.

D. WILLETT: Sure, great. That is not at all to de-emphasize the importance of the rest of it.

DR. ROSS: Along those lines, isn't such data collected by USDA in the continuing survey of food intake by individuals at CSFII? I just wouldn't want to give FDA the message that they should be doing something that is already being covered by another agency or might be appropriate to be done by another agency. I agree with you

that that would be good information to have, but I don't want them to be double-analyzing if it's not appropriate.

DR. WILLETT: It definitely would be important to work out anything they do in collaboration like they do, but in general, not much of that. The CDC and those other groups are not measuring fat and trans-fat; they're measuring in human blood samples. CDC is doing that. But you would also want to know where it's coming from, which is what this would provide.

So there is, on the sodium, in creating the database, some analyses done, but they're not enough to very well track things over time. I'll write that paragraph.

DR. RUZANTE: I was just going to go back to the questions here. I think a lot of the exercise that they are doing in trying to come up with those risk rankings for either the highest risk foods as well as the most significant contaminant -- by going through this exercise, they already should have this answered, what food or food products should be sampled, because they probably are like, okay, those are the food categories that we regulate and how we go about regulating those foods, so we have those categories. And then they are like, we cannot find data for A, B and C, -- and I didn't necessarily see in any of the presentations -- we obviously know that ranking risks

is a really data-intense exercise. You need tons and tons of data of good quality because, as you say, garbage in, garbage out, that kind of thing. You can put anything in a risk-ranking model, but what are you really going to get out of it.

By going through the exercise of putting together those frameworks and the methodology, FDA already has, I'm assuming, a clue of where they are lacking data and where the data is actually too old. So I'm a little confused about what we, as advisors, should say about this food or that food. I think some of those --

DR. HAYES: I think all we can do is base it on the presentations they made to us today and are there obvious voids or gaps that need to be filled. Do they really need to do rabbits in this meat thing?

DR. RUZANTE: Well, let's make something clear. This is FDA, correct? We are not going to FSIS. We are not going to be talking about meat and poultry, are we?

DR. HAYES: They made a presentation and it's part of this package.

PARTICIPANT: That's what I want to ask as well - what is our jurisdiction?

DR. HAYES: I think we ought to assume that that which we heard today is what we're responding to.

DR. ARMBRUST: The risk ranking that I'm

understanding, which is all under the Food Safety Modernization Act -- that effectively marries the two organizations.

DR. HAYES: It's all one package under that modernization act.

DR. WILLETT: Just as an interpretation of this question, I think we are not asked to actually answer that question. It's basically saying this is their statement that their process -- that should be their goal. I was first trying to answer that question but then I realized if you do look at the questions on the back, those are much more general. It's more -- is the process in place to answer those questions.

DR. HAYES: Yes, but I kind of want us to run through this so that we remind ourselves of what was presented to us today. Let's just jump to the next one.

Where in the food supply should samples be collected? And they told us they're doing it really from the farm, manufacturing, to the plate, taking it to CDC and actually doing human samples. So it seems to me they've pretty much covered the overall gamut.

DR. RANGAN: I think we need to be clear that that is part of our recommendation, that they do need to do that. I think we heard a little bit that USDA is starting to get on the farm. FDA has yet to get on the farm. FSMA

is going to be part of that, so I think that needs to become part of our recommendation.

I would just like to go back to the food question for one second because as we think about what they're sampling, I have a question about chicken fried rice and spaghetti and meat balls. I'm not sure what we're getting with that kind of composite food testing. I think as a way to prioritize -- and I don't mean to specify meat balls and spaghetti -- but if you're taking a food that's a bunch of different foods, what value does that point have in the end except that someone who might eat spaghetti and meat balls, maybe that one or not that one, may or may not get that exposure. I think there's far more valuable information to come from discrete food testing, whether that's the TDS, and it seems like it's more relevant to the TDS.

DR. HAYES: So you are suggesting possibly to eliminate a meal and to go with the meat ball itself and the spaghetti itself.

DR. RANGAN: That's correct.

DR. HAYES: I think one of you guys had a comment about that also earlier. Do you want to say anything?

DR. SWAIN: I agree with that. I think that testing the food itself rather than a composite meal or a food mixture -- it seems to me that if one has good data as to individual components and where they stand, one can then

make a judgment as to a mixture or composite.

I just wanted to add as well that I think it makes sense to test at these different stages. It brings to mind how maybe perhaps the processing or manufacturing procedures might in some way either dilute or concentrate what might be there. It makes sense to test at each of these stages. And I have the same questions when I think about testing in composite foods or mixtures versus discrete entities.

DR. HAYES: What I heard so far is that we're reasonably okay with the foods and food products that they're testing. We want to recommend, emphasize and encourage them to go from the farm all the way to the fork, but even really beyond where they're testing blood samples that CDC is doing.

Secondly, we're not sure that we agree with them testing meals. We would suggest they think about just testing foods *per se* and not prepared meals. Anything else?

DR. SHREFFLER: Can I comment on that? I think I agree with that notion when it comes to sort of the home-prepared mixture of foods, the spaghetti and meat balls that someone makes, but I just want to clarify what we think about manufactured meals, which are, for better or worse, probably for worse, a large part of the American

diet. So, in other words, the frozen entrée. I'm just clarifying what we mean about composite foods because there is something lost in terms of processing perhaps if we give that up, and particularly in the case of manufactured composite foods. Then there are issues of cross-contamination, et cetera, that you could miss if surveying only sources.

DR. MEYER: It seems like some of the hazards are introduced in the processing, because one of the slides they had showed that one of the most contaminated was a chicken salad sandwich. The one they found the most frequency of microbial contamination was a chicken salad sandwich, as far as the classification. So the processing itself is adding some of the hazard. That would justify looking at a composite.

DR. ARMBRUST: Having lived on the regulatory end of that world, I can tell you one of the issues you run into with chicken salad sandwiches is not so much the manufacturing -- that may be part of it -- but also just the storage conditions of these things that you buy right off the shelf. I'm not sure if that's where they were sampling or not.

DR. SHREFFLER: Then I guess the question is, is that relevant. Should that be within the purview, even if it is storage-related? Probably so.

DR. ARMBRUST: It does come back down to foodborne illness prevention.

DR. WALLACE: I hear the conversation over here and I can see where perhaps it makes sense, but I would like to challenge the committee with who is responsible for which stage of the whole process. Let's throw this back in the context of the FDA and the approval of drugs. What they approve and inspect is the final drug that is marketed, that is commercialized. If it doesn't meet the standard, then it's the responsibility of the manufacturer to back-trace where that contaminant, where the whole process went wrong.

So if we use that as the scenario for foods, then I would suggest that what we would agree on is that they would test the commercial product. If it doesn't pass the test, if it has too much residues, is it the FDA's responsibility to trace back the source or is it the manufacturer's responsibility to trace that source? It has to be done but whose responsibility is it?

Again, I'm looking at a finite budget of the FDA, and let's get the most bang for the buck. To me, we're regulating the commercialized product, not the process.

DR. McBURNEY: I think that we need to do some categorizations and sort of put them into buckets as we think about this.

If it may be for pesticides, I may choose to emphasize having carcasses, so a carcass of an animal or a chicken that is tested for that before it gets to the final product and saying that I want to know every time there's a finished product in the grocery store, that that has been sampled and tested.

Similarly, I might choose to have microtoxins or other things tested at the grain level rather than having it be a requirement of every bread or roll category product.

And then I would distinguish differentially, looking at microbial issues because I am concerned about it in the sandwich I eat, but I'm not thinking of -- I'm thinking differently about where in the cereal grain to flour to finished food do I need which pieces analyzed so that I know from that point on it's safe from an insecticide, a pesticide or a residue regardless of what goes on. And then, where might it pick up a microbial contamination.

Similarly, a carcass of beef or boxed beef is different than maybe a hamburger or a cold meat, sliced meat deli sandwich -- I don't think we want everything at the endpoint as in every finished product has to be inspected and examined across this category by the FDA.

DR. HAYES: Does this concept make sense?

DR. SANTERRE: Can I add to Michael's comment? Specific to meat products, and I've looked at this a little bit, except for drugs, most chemical contaminants, chemical hazards, get into our meat products from what the animal consumes, from what the animal eats or drinks. So we've got a point where if we really test feed and other things that are going into the animal, we can almost eliminate our problems downstream. Very little contamination occurs during processing, unlike pathogens which can grow along the whole chain.

So, relative to meat products, if we can really focus on feed for chemical hazards, we can eliminate all those problems downstream. In my estimation, we're not doing enough testing of feed --

DR. HAYES: What I would like to do is for the two of you to put together a short paragraph explaining this bucket concept and then we'll look at it, if you guys could work through that.

DR. LINKOV: The type of foods, the number of samples depends on the goal that you have. For example, my impression is that at least some of the programs have the goal of finding contaminants and drug residue and things like that. If this is the goal, you need to go to the most contaminated sites where you're likely to find it, and the idea is that if you do not find it there, probably the

whole supply chain is clean.

But I guess this issue of how you relate sampling strategy to your decision is not really dealt with; at least I haven't seen a link from sampling to decision, and probably that is what you could recommend -- to clarify better how these samples or sampling strategy will be used to make specific decisions.

DR. HAYES: I think it is a great thought. I think that's going fit on one of our questions tomorrow and we can make a recommendation on that.

DR. MEYER: On the bucketing you talked about, it seems like they're already using that terminology when they do classification, classification, pair. It seems like the concept is within what I was reading as far as the documentation.

DR. WILLETT: Just to add to that a little bit, I think it would be unfortunate to create rigid rules about this, but sort of deep thinking about what's appropriate to sample. Like the spaghetti and meat balls, the lead, it turns out, was from lead soldering of Chef Boyardee cans of spaghetti and meat balls, so you really do have to look at the end product in some cases to pick up some things. So there's no single right answer to this, and I think your point of careful analysis of each situation is important.

DR. HAYES: Scratch Chef Boyardee; we can't name

products.

DR. WILLETT: Sorry about that.

DR. RUZANTE: I would like to disagree with the approach of using the drug system as to food. I think we really need to have data along the chain, and I want to stress here that little is done at the farm. NARMS mentioned it is starting to look, so it's very important that we make it very clear that there is very little data collected at the farm right now for food safety.

DR. HAYES: I think we brought that up in two places. One by looking at the grains and then the recommendation to --

DR. RUZANTE: Yes. In the context of risk ranking, we heard some of the approaches are top-down where you look at what is the disease that you see in a population and then you sort of go down to estimate your risk and ranking. By having data from the farm at processing and all sorts of different points, you can then do the bottom-up approach where it's a different way of ranking that potentially can be more robust than looking at outbreak data.

There is a lot of value in having data throughout the chain for risk ranking purposes plus others.

DR. HAYES: Yes, and I think that was the point that you were making -- throughout the chain.

But let me ask another question. Is there a reason to suggest to the Agency that maybe they ought to think about microbial issues over here and the chemical issues over there, because they seem to be looking at the chemical issues in the same light that they've always looked at the microbial issues. And can you really do that?

DR. SANTERRE: Yes, I would agree with you. I think they need to be separated or separate acute versus chronic. I think it's easier because you're going to have different disciplines involved in monitoring and regulating one versus the other. So the first approach I agree to, but you could also break it by acute and chronic. Most of the chemicals will fall into the chronic.

DR. HAYES: I think the big issue is, with the exception of allergies, I'm hard pressed to think of any emergency room visit that a chemical causes.

DR. SHREFFLER: Like a reaction to histamine, some of the fish toxins --

DR. HAYES: That's, again, an allergenic response.

DR. SCHREFFLER: Well, it's a toxic response but it's a rare example. Maybe allergies should be their own bin.

DR. RUZANTE: But in separating both of them, if

you're talking about risk ranking and you're talking about an agency that says I want to rank the risk so I can put efforts and money into those, and not those. So if you have them separate, take the first 10 here and the first 5 here -- how do you try -- there has been an eternal discussion of can you rank microbial chemicals at the same time. Ideally, directly it would be great because then you have a single unit of comparison. But I understand the challenges.

DR. SANTERRE: Can I comment on that? It was a very good point. What we saw today, when I looked at this, I would say that the chemical hazards are totally out of the equation because you won't have bodies in the streets or heads in the toilets to count. We don't have that with chemical hazards. We have potentially 30 years down the road. If the Agency is looking at whether we still measure chemical contaminants and follow it based on the approaches we heard today it would totally fall out of the equation because it would be lower priority than the pathogens.

That's the challenge -- keeping a mixed portfolio so we can cover various things, in my opinion.

DR. RANGAN: I just want to say a couple of things if I can. One, I take your point about testing composite food for what packaging may be doing, and I think that's an important element, and I think BPA for some

reason was left off this entire presentation, but I'd like to throw it back on.

The other thing, Kendall, to get to your point, pathogens start in manure and then move all the way through the food system, so whether that's going to go on to a meat product, whether that's going to fertilize a crop and put it under FDA jurisdiction, that's where it's starting.

If we as a committee are thinking about risks, I hope we as a committee are thinking about mitigation because that's the end goal, is how do we reduce these risks over time and how do we eliminate them, hopefully. And HACCP is part of that, and I think whether it's drug approvals, FDA does have jurisdiction all the way back in the chain. It's not just the manufacturer, and it's not just up to them.

If we are thinking about where those critical control points are on produce farms, for example, where there are none -- there are no standards for manure right now, there are no standards for compost -- we're not dealing with the root cause of the problem, and that's what we do need to be dealing with. So I think it's well within our purview to go back that far in the system.

DR. ARMBRUST: One thing I'll add on top of all of this, too, is that you have to realize that in a lot of cases, it's not FDA that's necessarily going out and doing

all this work at the state and ground level; it's usually the state departments of agriculture and state departments of health that are working, in some cases, under contract with FDA and operating under federal authority on that basis as commissioned officers. Or, in many other cases, they're acting under state authority.

So, when you talk about a lot of this data being generated, some of it is FDA money but also some of this is coming back at the state level, too.

Getting back to the feed, for instance, states actually generate considerable amounts of data on this. They put out a lot more data on it than FDA. Is it all readily available? Not necessarily, but it's also within certain areas, too, because certain types of, for example, the feed microbial toxins, you'll get some of those in some parts of the country and more in others.

It's not a simple system but that's part of what the Food Modernization and Safety Act is doing. It's really bringing the states and the federal government together, working under partnerships so they can share data and they're not having to go back and duplicate laboratory data again.

I think there's going to be a very big push in that area.

DR. HAYES: That really leads into 3, 4 and where

should samples be collected, are they doing it in the right places. You raised the question sampling is going down. Are they collecting enough samples to be analyzed? How many samples need to be collected, and are they analyzing for the right things, based on what we heard today?

DR. RUZANTE: How many samples need to be collected? What is the goal of the program? What are you trying to do? Are you trying to detect violation? This is one way to sample. Are you trying to determine prevalence so you can then try to estimate risk and then do a risk ranking? It depends on the goal.

DR. HAYES: And out of the presentations today, did you detect a goal?

DR. RUZANTE: Well, it seems that what they're trying to do is basically catch violations, which I'm not sure if all the time it reflects what is the prevalence of the levels across the board. It also seems that the numbers they are sampling seem to be way below what could give them some confidence that that is what's out there. How many samples need to be collected --

DR. HAYES: Am I hearing from you that maybe they're not collecting enough samples?

DR. RUZANTE: That's what I heard today from them, it seems like. Resource issues and --

DR. HAYES: Is that kind of a general consensus?

We're not getting enough samples?

DR. LINKOV: Of course, we always can say why don't you collect ten times more samples. They don't have the budget. I think the whole effort is to prioritize. But I think the disconnect is that the goals are not clearly set. You cannot say you have enough samples or not enough samples if the goal is not set.

I agree, if your goal is to catch violation, you do one type of sampling and you collect X number of samples. If your goal is to do risk analysis, then it's a very different story, but I don't think risk analysis is possible for emergent chemicals no matter how many samples you collect. It's a question of judgment. The nature of the emergent chemical is that they don't show up until they show up. You cannot predict where they are and when they are there.

So it's a very difficult story here, and that's why you need to start not bottom-up; let's collect as many samples as possible and then figure out what to do. But rather, top-down, and say what is the mandate here, and from the mandate say they are going to meet this mandate by making this type of decision model, and from that, figure out what samples need to be collected and what is the value of collecting more or less samples specifically to this goal.

DR. ROSS: My hearing of the presentations this morning was not so much that they're attempting to detect violations as to how a working surveillance system is in place which will detect violations in the process. But I think they're trying to do surveillance, and I think they're also very sensitive to the fact that they can't do everything so they want us to help with prioritization.

One of the things I'd like to suggest as a general message is that they use the very extensive data which they already have -- gaps admitted, but nonetheless, very extensive data -- to inform their decision about what needs to be measured at what frequency. I think in the total diet study they're probably analyzing some things over and over that are pretty stable over time and other things need to be measured on a more frequent basis.

Another model that comes to mind is in NHANES where the things that are analyzed over time change so there are certain measures that are made every time NHANES is run, but there are others that kind of come in and out of the survey depending upon their significance at the time.

So I would like to encourage a flexible model, encourage them to use their knowledge to be able to be more flexible in their approach.

DR. HAYES: Can I get you to put together two or

three sentences, no more than a paragraph, on just exactly what you said so we can add to that?

I don't know whether you had similar thoughts?

DR. SHREFFLER: Yes, I largely agree that there were examples where they had very specific objectives. The antibiotic resistance program maybe is one of them. I did hear a lot of call upon us for help stratifying -- not stratifying risk in this case, but stratifying how to allocate resources.

DR. SANTERRE: I think there are different scenarios that require different things, and I agree with Cathy's point that the surveillance, the way we're doing it is pretty good. But I would propose that there are some high-risk contaminants out there like the PCBs that we saw in Belgium and Germany recently that need to be analyzed not at $1,000.00 per pop but with a low-cost screening method to protect the public health.

I think in some cases you want to do your surveillance and you want to see what people are exposed to, but on the other side you may want to categorize some chemical contaminants that are just pretty challenging and very expensive if we have to deal with them, so we'd like to screen more samples and try to have a tighter safety net. So it would be two different approaches I think.

DR. ARMBRUST: One recommendation I would like to

see is -- because long term what's going to end up happening is they have to go back and re-evaluate this process every 2 years. As they start getting more data, as you start bringing state data online, you're going to see changes in terms of -- you get more data, you're going to get more information and you're able to go back and refine how you're doing your risk assessments and if that is actually the right way.

So one thing I would like to see recommended to FDA is to really try to accelerate the process of getting the states onboard, working with the states and really increasing those partnerships to increase the overall datasets. And I will put together a little paragraph for you if you want.

DR. RUZANTE: And industry, for that matter, as well, if possible.

DR. ARMBRUST: Exactly. That's the other partner that is unmentioned in FSMA.

DR. WILLETT: I think there is a fundamental question here that I don't understand the answer completely; maybe others do. The one set of calculations in the document was the number of samples required to detect the 1 percent prevalence of contamination, which works fine and it came out to be somewhere around 300, depending on what confidence you wanted in that answer.

That works fine if you find no contamination. Then you can say it's less than 1 percent.

But in quite a few examples there was 1 or 2 percent contamination with something. Well then, how do we interpret that? Is that acceptable? What do we do? That may be a flag, if it's PCBs, to go out and analyze PCBs much more extensively.

But is the level of contamination that they're finding acceptable or not? I think that's a fundamental question. Some people would look at this and say, oh, my goodness, 1 out of 100 times I'm going to be poisoned. Of course, that's probably over-interpreting that, but really, what is acceptable there? I didn't get a feel from the presentations.

In general, I was somewhat reassured that somebody is watching the store for most of this, but what do these 1 percent levels of contamination mean? The violations -- clearly, this isn't looking for violations because you can't look at 800 samples for all of the times that people eat food. It's hundreds of billions of potential samples and we're only looking at 800 so it's giving a snapshot, a little bit of an overview about what's in the food supply.

But I'd like to hear from FDA, how they are interpreting these levels.

DR. McBURNEY: I would like to go on record to say I commend them because I think we've got the safest food supply in the world and they're doing a really good job of trying to deal with the resources they have, and commend them for seeking guidance on how to prioritize use of those resources.

DR. HAYES: Would you be sure to include that, because we do need to commend them in the very, very beginning. You're right.

DR. McBURNEY: Because they are doing that, and we do have a very safe -- and we live in a world that will never be 100 percent safe, and we want to give them guidance on what's the best way to do it. I think the biggest part that we haven't even talked about that is on the table is that we eat relatively little that is domestic food.

Most of what the organization has been structured for is really based on the grown here, manufactured here and consumed here model, and increasingly we live in a world where it's coming in in an imported form which also changes what work needs to be done and where those resources need to be allocated. And that's what people are choosing to do and we need to help them be empowered to continue to give the confidence that we want because if there is, and when there is, a situation, everybody will

say they haven't done their job.

DR. WILLETT: I think we should take out the phrase "we have the best food system in the world" or the safest food system, and we should commend them. But I was actually wondering if somebody had actually done an analysis of imported versus U.S. contamination. My eyeball impression was that the imported food was less contaminated than the U.S.-produced food.

DR. SANTERRE: So, historically, FDA has looked at pesticides, for instance, imports versus domestic, and typically most of the violations coming in from abroad are a pesticide that's not approved in the United States showing up in one of the products they tested.

But the products are equivalent -- imports for pesticides versus domestic. We were a little lower in the last one I looked at, but every year they tracked it, it was pretty close to the same.

DR. ARMBRUST: We've seen a bigger problem with seafood coming in from certain parts of Asia. I can tell you about the number of stop-sale orders I signed off on in Mississippi.

DR. MEYER: I would like to reinforce what Cathy said, and I felt that the reason we're sitting here is that, yes, they are doing a good job but they are under mandate now to do a better job, and they sense they need to

change some things in not only efficacy but in efficiency. And they're asking our guidance to help them and they want to move, I think, to some sort of a risk assessment model to do the prediction of what to sample to get that efficacy and efficiency up. I thought I saw three different proposals -- not proposals, but three different descriptions of how they're doing it now as far as making that prioritization, some of which involves differentiation of different roles of the different agencies, and the good thing was you sensed that they were talking to each other.

So I don't see any reason why that should be changed. I think USDA belongs on the farm and I don't think FDA needs to go there and sample if it's already working, as long as they're talking to each other.

I saw sort of a qualitative assessment of where the priority should be. For example, there should be a focus on what children eat. I don't know that there's quantitative data that backs that up but there is a political sense that we need to protect children. So it fits in with other toxicology aspects that are going on now.

The other is the statistical methodology which draws from the historical background, which was emphasized before. I'm not sure I understood all of that, but it is a good plan I think. So I think that's really what they want

from us, is just maybe not an endorsement of what's already going on but, having understood a description of what's going on, whether we approve that or whether we can recommend a better way to do that.

DR. HAYES: Wasn't the vast majority of what we heard today the exposure side of the risk assessment equation, because they really didn't talk about hazard in the classical sense. It's mostly exposure and how do they get the exposure data, which I think is key to the risk assessment question.

DR. MEYER: Well, I think there's a reason they don't talk about hazard, other than the microbial sicknesses which are immediately apparent. I agree approaching the chemical risk is going to be very, very difficult.

DR. RANGAN: I have a couple of things I want to mention. First of all, I think we should be promoting as a group the use of these rapid assay systems so that we can collect as much information as possible. Sometimes, I think, for efficiency's sake, we have to combine micro and chemical together because otherwise we're doubling the number of samples we need for everything. For efficiency's sake, I think it is good, where we can maximize, to do the testing --

DR. HAYES: I don’t think we're saying don't do

your analysis on the same sample.

DR. RANGAN: I just want to be clear about that.

DR. HAYES: It's once you get the information, how do you handle it.

DR. RANGAN: Fair enough, and I agree acute and chronic hazards have to be handled a little bit differently. But from the sampling point of view, I think there's some consolidation to be done.

The other thing I know we spend a lot of time on at Consumer Reports is segmenting across production practices, and there are a lot of different alternative production practices out there. There's organic, for example, which is run by the USDA. You can't use antibiotics in it. Why aren't we really paying close attention then to antimicrobial resistance as it relates to those production practices to see if they are potentially good mitigation strategies, or maybe they're making things worse?

What about grass-fed systems when it comes to meats? I think there are a lot of different things we can be capturing off the food we're testing to help differentiate among alternative production systems, again getting back to mitigation strategies for risk.

The last thing I want to bring up which is different is what not to test. I'm generally not a fan of

not testing things because I think it's important, but my colleague and I were sort of pouring over the seafood data. We have hundreds of data points for albacore tuna and mercury, for example. We have 800 data points. Those levels don't really change; they haven't changed much in 20 years, so maybe that's a good place to start with reducing testing on albacore tuna and increasing testing on other seafood or other items where we don't have enough data. I think that's one strategy for helping keep the resources and add efficiencies to the resourcing.

But I think there are contaminants that are not going to move much over time and we have enough sample points out there. We probably don't need to keep on testing albacore tuna for mercury.

DR. WALLACE: I think I will take it a step further as far as where we can improve the efficiencies and go back to the discussion where I suggested the FDA testing the end product and leave the responsibility of the manufacturer to test the individual stages.

What I don't want to see us doing is mandating testing at every single stage, because there are some tests where you may see the microtoxin in a sample that doesn't make it through the manufacturing process itself and show up in the final product. For example, in the manure. Of course, you're not going to test manure, and if you see a

positive signal there, you're not going to ban that necessarily from the final product.

I think the challenge for this committee is identifying pinch points where if you find it in the meat, then it's probably going to end up in the final product. If you find it in the grain, a pesticide, it may or may not end up in the final product.

I think the real challenge is not to treat everything the same but to recognize that with each scenario or group of scenarios, there may be certain pinch points where we can improve efficiency by testing at that stage and not necessarily at every stage along the production line.

DR. SANTERRE: Or the feed. In some cases it could be the yellow grease that came from restaurant oil frying that went into the feed. I agree 100 percent.

One of the challenges -- I think to Sharon's earlier point -- is there is a line between agencies that has been getting better because of good professionals both at CVM and FSIS, but I think that bridge still has to close. FSIS does not have authority to go onto the farm and investigate anything that happens there. They can't look at it until it's a carcass hanging in their sheds, generally. So that communication really has gotten better but I think it has a ways to go so that those two agencies

really are hand in glove at least for animal products.

DR. MEYER: Maybe that should be part of our record, that we encourage them to continue to improve that relationship.

DR. HAYES: Good point, and we should keep that as one of our recommendations. You guys are working together, but you can always work together better.

DR. RUZANTE: Yes. And USDA cannot go to the farm. FSIS cannot go to the farm, but they could, for example, sample incoming live animals to have an idea at least of the incoming load of pathogens, for example.

DR. SWAIN: I just wanted to say and clarify that I support testing as resources permit at whatever stage to require additional data, but I do support testing of the final product, the foods that are consumed and sold at retail.

Earlier there was discussion relating to imported products. Every few years the landscape changes drastically; it's a very dynamic food market that we're in. When I travel internationally and look at food labels and see what is on those labels and think of all the imported products, it also makes me think about additives. And when I think of additives, one of the major additives in the United States is sodium, sugar and others. But there are a number of other additives that are added to food in

significant amounts that are not on the GRAS list as generally regarded as safe or recognized as allowable in the United States; yet, I've seen packages at many international markets that still are getting through.

There are additives out there that are also unregulated. So I'd like to see something maybe included in the wording, and I'm happy to assist in any paragraphs that are provided. But I support testing at the retail level as well.

DR. McBURNEY: Walt is probably not going to agree with me on this, but I was really surprised and I'd like to see something done with the total diet study. First of all, I hadn't realized its inception was built around radioactive testing. I'm not certain that testing from three cities and four regions is really a way of doing radioactive testing.

I also think we need to know what the foods are, but there are other programs like the toxic elements looking at pesticides -- things we definitely need to know in the foods we eat. But having foods selected from a few marketplaces and then being prepared in accordance to what is current tradition with data that may be 10 years old I don't think is the best use of resources.

DR. WALLACE: May I just add to that the question I brought up as far as metropolitan versus rural types of

diets. I would expect pesticide residues in any given grain may be quite different in the diet of individuals that are living in large metropolitan areas versus off their own farm. That is just an assumption.

DR. HAYES: How much has changed with the large increase in ethnic expanding populations and their diets? Are they taking any of that into consideration?

DR. McBURNEY: One of the concerns very well could be that with a lot of people choosing to eat local, there are more heavy metals if they're growing crops or plants that they're eating from gardens that are in urban centers and aren't raised. I think there's this perception that that is always healthier but it may indeed not actually be healthier.

DR. HAYES: And I didn’t hear anything about arsenic in rice today.

DR. RANGAN: But I'm going to bring it up right now. I just want to go back to manure for a minute because that's part of arsenic in rice, too, and the issues there.

I think, without standards, you're not controlling pathogens adequately in manure. When they go on to another farm and you're fertilizing crops, those crops can take up those pathogens. There are studies showing that spinach can take it up into the leaf. The cantaloupe that has Salmonella -- you have to look at all

those things, and manure is one of the root causes so I think you do have to test at that point. And you need to do it for microbiology at least until you identify the critical control points that you're going to need to mitigate that.

Then there are things like heavy metals which don't get composted out. If you're feeding the chicken arsenic and you're taking that poultry litter and fertilizing rice crops with it, you're contributing to the burden of arsenic going into that crop production.

So again, looking at heavy metals and the standards we have for those and making sure that we are mitigating those practices as best we can is also very important so that we're not cycling these contaminants in our food supply.

I just want to emphasize that manure is very, very important when it comes to contaminants in the food supply.

DR. RUZANTE: Yes, and I would emphasize that the data -- you really need that data there when risk ranking because this task is about risk ranking.

DR. RANGAN: FDA already put out a notice for compost standards under FSMA, so that will be the first that FDA is actually even going to address it, but it has not been addressed up until this point.

DR. ARMBRUST: Various states do have compost laws and compost rules but I don't think there's anything comprehensive federally. But there are a number of states that do.

DR. RANGAN: Organic is the only one that provides a federal standard for composting, under organic, and what has to be done in order to use it.

DR. WILLETT: Since you raised the total dietary study, it would be desirable to have barter-based sampling, but it is a trade-off with budget. If anything, I think the U.S. supply is becoming more and more homogenized and in the rural areas people are shopping at WalMart, for better or worse. They're shopping at large grocery chains, for better or worse. I think it is the best way to look at the overall time trends of what is going on.

There are also some trade-offs to keep the foods constant, and at least then you know what's happening to the composition of the foods themselves. But over time, they're doing it at about a 10-year cycle, re-adjusting the mix of foods that would take into account Hispanic diets and other shifts in the food supply.

So, given the compromises in what I understand is a pretty small budget for that program, it seems like it's an important part of the picture of what Americans are eating.

DR. ROSS: I would like to support that comment. Michael, you were saying something similar. Maybe the way to phrase it -- first of all, I think the total diet study is important and has been a good source of information, so I don't want to make it sound as if we think it's unimportant. But we could talk about modernizing the strategies for sampling.

For example, in these four different regions, they might be sampling exactly the same product four times because it's all coming from one original source; whereas, there may be an opportunity for sensitivity to the distribution system of foods in sampling in different locations or different ethnic groups, et cetera.

I guess I would just put it in terms of modernizing their sampling strategy to take into account the changes in distribution of foods and what people are eating.

DR. LINKOV: Again, with radionuclides it was interesting because I did (?) but I remember that they all correlated, so measuring all of them doesn't make sense if you're trying to detect presence of radionuclides. I think it's very expensive to measure cesium.

Again, what is the goal of measuring all radionuclides? If the goal is to detect radioactivity, then probably one is good enough to screen if you like to

consider resources.

DR. HAYES: I would like for us to jump down to the second series of items in 5 and 6 -- how or whether to group or aggregate foods; whether to bin or aggregate hazards. Did they cover that to everyone's satisfaction? Are there any comments about those two items?

DR. RANGAN: I think you have to be very careful about binning, and I think you have to have some consistency in the data in order to bin it. Rice, for example, arsenic on rice, those levels are very, very different depending on the geographic location they come from, and that is intelligence you want to integrate. So, bin the ones that are from a certain region, but I don't think you can bin all rice and make much sense out of that, especially when, again, you're trying to get to mitigation.

DR. ARMBRUST: I would just add, too, going back to the example that Urvashi just said, that's going to change depending on how it's grown. As practices change, any process that they use for aggregating or binning needs to change as technology changes. So that's something that needs to be taken into account when they re-evaluate the process they use every couple of years.

DR. RUZANTE: A couple of thoughts here on those. First of all, I think the consumption data needs to be updated -- the NHANES data on general consumption from 2003

to 2004, and I believe CDC also has food survey consumption data from 2007. Some of the results that come out based on consumption, assuming consumption nowadays and trying to rank risks on old data, you can arrive to a series of mis-assumptions I think.

A good example was, I think, raw kale. It was assumed that no one eats raw kale and everyone cooks kale and I think those were results that came out of FSMA and I think maybe we were using consumption data that was too old. No one used to eat raw kale, but nowadays, raw kale is everywhere. I'm sure everyone sees raw kale in all sorts of salad. And it was exempt for FSMA.

I worry -- obviously, we have to have this balance about testing and sampling, and resources are small, they are not endless, and the agencies obviously are very careful and those kinds of things. But I think consumption data on a more broad scale needs to be updated, urgently. FDA also can look at other private-owned datasets. I know certain marketing companies track consumption data. But this is critical I think to calculating risk.

When it comes to what data sources, there are data gaps, and I think updating consumption data is critical.

There is also some consideration on what factors

or criteria should be included in a risk-ranking model, or if other factors rather than public health impact should be considered. My recommendation would be that FDA and FSIS should try to organize a representative group of stakeholders to address those questions in a way that could be representative of the groups of interest. That would even work for weights, the question of how weights are -- Igor, you are probably more familiar with this process than I am, but I think that's the way they should go forward with that.

DR. HAYES: Other than public health, are there other things that should be considered as far as risk prioritization by the Agency?

DR. RUZANTE: I think the answer is yes, but I think it needs to have a more systematic and transparent approach that takes into account stakeholder groups to come up with that.

DR. HAYES: Can you give me an example?

DR. RUZANTE: I think feasibility, obviously, of a control measure. For example, you can have risk but you have no control measure on earth for that type of risk. Are you going to rank high? You have nothing to do with that. I think you could have economic impact; you could put consumer perception; you could try to capture what people are thinking. You can think about policy

implications like trade implications. I think BSE was the classic example where the public health risk was very minimal, trade issues huge -- jump on priority up there. So I think we know for sure that decisions are made more on public health risk.

But what criteria then I think it needs to have a more representative process.

DR. HAYES: Isn't that really getting into risk management as opposed to putting risk within the Agency and priority?

DR. RUZANTE: But prioritization is sort of a risk management tool. We have one here --

DR. HAYES: We're going to get into that. Don't jump down to that yet. I want to stick with these others first.

DR. LINKOV: The risk management, the risk assessment separation is very artificial, so we cannot talk anymore about risk management and risk assessment in isolation.

DR. SANTERRE: I would like to recommend some flexibility. After the meltdown in Japan, I think they tested a lot of product and I don't think they found anything of a health risk. But the Agency, I would guess, doesn't feel like it has the ability to drop a program in the middle once they find nothing, or to say, okay, let's

look at fish 2 years now when those fish might start getting into the market.

I think there needs to be some flexibility with things like melamine, acrylamide, where the Agency can run those down as far as they have to, and then when they realize there's nothing panning out, they've got the data they need, drop that effort and go on to something else. I think some of their resources need to be flexible so that they can adjust to changing situations.

I think the sense, when you read their reports, is they lack that flexibility. They have to stay in a program for a year at a time and not drop it.

DR. HAYES: Any other comments or thoughts about these first six and the second A before we move on to the real questions?

DR. LINKOV: I guess for risk-ranking tools, we had two presentations today that started getting to what I would characterize as multi-criteria decision analytical approaches to the problem. I am concerned that in a decisional analytical approach you have technical data populating structured criteria metrics, but also you need stakeholder input on weights associated with risk criteria and the importance of this criteria, and I think a couple presentations you had really struggled with these issues.

I think there are two ways of doing that. One is

for FDA to decide what would be weights they would like to have on this criteria based on their regulatory mandates. The other way is to really get the stakeholders and see what would be the space of solutions and prioritization that stakeholders would drive, and then see how the ultimate prioritization of chemicals or whatever they use would be affected by different rank categories.

This is a very important design issue that needs to be addressed.

DR. HAYES: You just won the opportunity to put together a short paragraph because I think that's an important issue that we need to at least bring back to the table tomorrow.

DR. McBURNEY: I guess the only other thing I would add, because I feel strongly about this in other parts of my life, is I think there should continue to be sampling not just of what people consume but really of nutritional status -- taking blood samples to look at what might be levels of some of these within humans as well. In many of our situations in the past we have identified, because it was an outcome effect and then worked our way back to identify, what was the compound that was being ingested and where was it coming from. Because it's not always national; it may often appear in certain regions or in certain sub-populations.

I think that is as important a way to look and monitor as it is to try to sample all of the foods of everything that's being eaten throughout the food chain.

DR. HAYES: Let’s move then to the five major questions -- go ahead.

DR. WILLETT: I completely agree with that point, but I think there is a sharp line between FDA and CDC on that issue, so clearly, increased interaction and collaboration is always desirable.

DR. HAYES: And I think it's one of the things we want to recommend, that they're doing a good job but they can do a better job.

DR. LINKOV: Just a little addition on what to measure. Everybody seems to be talking about (?) materials. I didn't see them on the list but I'm not sure if FDA is looking into that or not. But it's something to think about.

DR. HAYES: We have five questions that we have to respond to and come up with some recommendations. It is now 4:00 o'clock and we have about 45 minutes today, and then we've got tomorrow morning and a little bit of the afternoon. It would be nice if we could look hard at one and two and see if we can come up with some thoughts that Karen can take down for our recommendations.

The first is: What factors, considerations or

criteria need to be considered when selecting which food contaminant pairs should be sampled and tested? Are we all clear on what a food contaminant pair is? Is there confusion? I'm still a bit confused. I think a food and a contaminant make up a pair, and some foods can have multiple contaminants.

DR. SANTERRE: Would this be like Salmonella in chicken? This is coming from the microbial side. Does it make sense on the chemical side is my question. I would just pose that question. I don't see the logic in food contaminant pair.

DR. SHREFFLER: You would have other applicability -- mercury in tuna, aflatoxin in nuts.

SANTERRE: But does it give you any advantage to pair those? You can still deal with peanut allergens --

DR. SHREFFLER: Seems to me it's just a jargon term. I'm not really sure we'd have to understand what that means to answer the question.

DR. MEYER: I think it is important to prioritize. I think that was the discussion we had here, that it's important to prioritize.

DR. SANTERRE: Let’s take melamine, for instance. When melamine started to show up in infant formula, milk powder, where it wasn't expected, if it was not paired, we may not look there. So the problem with doing a pairing is

you have to go through a process to develop the pairing which may keep you from seeing --

DR. MEYER: Right. It's all going to be retrospective -- I mean it's based on retrospective. You know arsenic appears in rice because there are areas that are rich in arsenic where they grow rice. You know PCBs will appear in oil products because it's fat soluble.

Another thing, too, is this has to be science based, and those kinds of arguments and justifications are going to be important.

DR. SANTERRE: What about mercury in rice? It's not logical.

DR. MEYER: I don't know the rationale. Maybe someone else can come up with it.

DR. SANTERRE: But we would never have paired those two together is my point.

DR. RUZANTE: I think it's important as a first step. You need to start with food pairs, and I think one important thing that you bring up is what are the unknowns, what are the emergings. The same thing happened for microbiological contamination. A lot of times you wouldn't expect to see listeria showing up in cantaloupes. CDC has a list of famous -- like in the last 10 years they saw all those outbreaks of associations of foods with certain pathogens that they would -- some they would predict but

some they would not.

I think you need to draw a line somewhere, but it's not that by drawing the line there you are forgetting that you are going to have associations in the future that are going to come up, and you need to find a way, a mechanism somehow around your risk ranking where you account for some of those things so that you have other mechanisms to keep an eye on what is emerging and what is unexpected.

DR. HAYES: When you start pairing foods and microbes, what do you have -- 25 max microbes?

DR. RUZANTE: No. You are going to have a lot more than that.

DR. HAYES: I am just saying about 20 pathogens.

DR. RUZANTE: Well, you have 31 pathogens.

DR. HAYES: All right, 31. Less than 100. We've got 600 pesticides; we've got 500 mycotoxins, 2,000 industrial chemicals that are there. It becomes harder, because of the numbers, to pair.

DR. RUZANTE: Sure. But then again, is there a way that you can bin those? I think this is also one of the questions. Again, there is a huge difference between microbials and chemicals, there is no doubt about it. They are equal in nothing, zero. If there is a way to put them together, if you're thinking about a prioritization

exercise, this would be beneficial for decision-making for allocation.

Is there is a way to consider chronic, because pathogens also have some chronic conditions. Not like cancer that's going to take 30 years to show up, but there are some consequences that come down the line that are not necessarily acute.

DR. WALLACE: I am trying to make things a little simpler for the committee. I don't think we're being asked to identify the pairs. We're being asked to identify what factors, considerations and criteria. I'd like to start off with, let's say, exposure. That should be a very important factor that should be considered in identifying which pairs should be sampled.

DR. McBURNEY: To me, there is a difference in the chemical versus microbial. I would encourage them to continue the multi-component or residue analysis because I think some of that terminology comes from the historical where you could only run one assay so you were limited in how quickly you could survey. But if you can do 600 on everything you don't have to really think about the pairing for the same reasons.

DR. WILLETT: I think their new plan that they're implementing is moving away from the pairing for their broad screening, and I think we should congratulate them

for moving in that direction. But that is sort of a screening. If there are identified contaminants in certain foods then you might want to do a much more extensive paired analysis, which I think is a logical way to go.

DR. HAYES: Let me carry us back. We've got exposure as a criterion.

DR. SHREFFLER: I heard a few others from the group. One was variability, so either geographically or over time if it's very low you can maybe test less. Alternative production systems, perhaps in favor of just simple geographic. Urban-rural divisions instead of just major cities around the country.

And the point that some contaminants correlated very tightly, so it may not be necessary to test multiple nuclides, for example. There are probably other examples.

DR. ARMBRUST: I would add, too, on the criteria for selecting food contaminant pairs the populations that are consuming them. If you've got susceptible populations -- for example, you have certain foods that are consumed very heavily by infants and young children and toddlers and they're going to be more susceptible than somebody like me or any of us.

DR. MEYER: Maybe we should encourage the multi-chemical analysis that they've been emphasizing so that we can uncouple a pairing. We can get an array. It would be

a food array rather than a food contaminant. An array of contaminants. That would increase efficiency.

DR. ROSS: It would be more like rice and metals rather than rice and arsenic.

DR. MEYER: Exactly, a class. It would be defined by the analytic technique. On the multi-chemical they're using a mass spec so they're picking up a lot of chemicals, but they could also use ICP for many different metals simultaneously on the same sample.

If we could encourage those multi endpoint assays for any given chemical class, you would actually get a lot more bang for your buck I think. I'm not sure if the multi-component was the $1000 assay they were referring to or not. Whether that would add cost if you did have a quick screen that was a luminescence -- I'm not sure. They would have to understand that because they know their cost-effectiveness. But we could maybe encourage a more efficient way of analysis.

DR. HAYES: One of the things that was raised in the next to the last talk was the unknown peak. How much should they look for things that we don't know about? Would that have helped them in the melamine situation?

DR. MEYER: They should have been able to pick that up with mass spec. Unknown peaks are not that unknown with the mass spec I think.

DR. RANGAN: They are already using that in the TDS. Those metals I think are screened as a deck, so they're already doing that.

DR. HAYES: I'm questioning. You get a peak, you don't know what it is on your mass spec, and it's a big peak. Should we encourage them to follow those kinds of things up?

DR. SANTERRE: I saw a presentation from an FDA person 2 years ago and they are doing that. It's very time consuming and very laborious to go through and find each peak and then identify it, and there are 100,000 to 1 million.

There's a researcher at Emory right now, Dean Jones, who is doing this with biological samples where he's getting up to 100,000 chemicals and he expects to get to about 1 million, and he doesn't know what those are. They basically just go in and look at all the peaks and then try to look for anomalies from one person to the other and do it statistically as opposed to trying to go the other way and identify each of the peaks and then find a problem.

It's a novel approach just to scan for everything.

DR. SHREFFLER: It does get to the question of how to select, and I guess we could recommend the methodologies that favor richer datasets, even if they're

not analyzed at that time. In other words, you don't have to pursue every peak at the time because it's really an analytical question at some point, at least for some methodologies. If you're doing mass spec on everything you'll get a bunch of unknowns, and then you could subset when something emerges.

DR. MEYER: If I remember the melamine story, it didn't become an issue until there were health effects. Was it in our pet food and in the Chinese milk? There were health effects and then it was chased down.

DR. HAYES: Yes. Proctor at the time had a pet food company, and they're the ones who discovered it. It was not just melamine but it was cyanuric acid.

DR. ARMBRUST: Both of them were being used as surrogates for protein because what you're trying to do when you analyze feed for protein, you're looking at just proximate analysis of nitrogen. If you use cyanuric acid and melamine --

DR. HAYES: They use -- and that gives you nitrogen, and they were giving you nitrogen.

DR. ARMBRUST: Both melamine and cyanuric acid have them, and what happened was when they started getting a protein manufactured that actually had both of them, when you put those two structures on top of one another, they'll actually form crystals. And when that was doing it in the

kidneys of the animals is when they started having problems.

DR. MEYER: I doubt that you're going to catch many unknown peaks without a really large commitment of resources, and I don't think that's where they want to go with this. But you could have things archived so you could come back around quicker based on the health effects that they would see. If you can keep these scans, keep these spectra.

DR. McBURNEY: I think the mandate I heard discussed was really about protecting the population and surveillance, so I would rather guide them to stay with the known risks and do more samples, and be able to look more at some of the other issues in terms of exposure, regional variability, and do that with the known because you can do more of those faster. And then, if something crops up, you can go back to look at it, or then you can expand. But stay with the known risks and sample more broadly.

DR. WILLETT: I think that while we are not meant to come up with an exhaustive list of pairs, I think one of the roles of this committee was to maybe put on the table some things that might not be on this list already for consideration. I heard BPA being one of those, which I agree would be worth just asking if that is being considered.

On page 119 of this big handout they have the growth hormones -- estrogens just for growth promotion, and I would just like to add are they also looking at or considering other growth-promoting hormones that are used. Obviously, the pair would be the animals in which they are used. There should be some monitoring of that. Maybe there is, but it wasn't on the list of things that they're looking at now.

DR. HAYES: Anything else on question one?

DR. SANTERRE: I would add the source of the contamination is something that's important. How is the arsenic getting into that? What is the way that things are becoming contaminated? That actually might help us to deal with the issue and know how isolated it is. Is it in a small geographical region like ball clay going into catfish feeds, or is it something that impacts all parts of the food system.

DR. MEYER: I would only do that, though, if your levels tested out to be above a threshold or regulatory level. They're going to pick up trace levels of things and I wouldn't recommend chasing them.

DR. HAYES: And again, rice is an example. There's high arsenic in the water in Arizona and that area.

DR. MEYER: Right. If you find PCB in an oil sample, you want to find out where it's coming from now.

Well, PCB is not a good example, but arsenic is. If it's trace, it's probably again a limit of resources.

DR. SANTERRE: Definitely agreed, but I think PCB is an excellent example, at least from the European. How did it get in there? It was an industrial oil that was either intentionally or accidentally dumped into an animal feed. If we could know the etiology or the source --

DR. MEYER: In that case, there would be no threshold; that would just be bad all the way.

DR. HAYES: Another example is the methyl mercury in the seed that went to Iraq or Iran and got there after the planting season so they just consumed it.

DR. SANTERRE: They made bread. Yes.

DR. WILLETT: Just so it gets in the notes, I think the point about other characteristics of the food, to be able to include in the data analysis whether it's organic or not -- I think that should be pretty easy to include. You had some other characteristics.

DR. RANGAN: Yes. There is grass-fed, there's a lot of different certification programs that are credible out there. We rate all of them. They can be captured from these food products so we can gain some intelligence about how those impact the contaminant levels.

DR. HAYES: Is that worth you putting together a short paragraph?

DR. RANGAN: I've been waiting for my paragraph.

DR. HAYES: Okay; you just got it.

DR. ROSS: This might fall under a consideration, but I wonder if it might be worthwhile to encourage them to do more analysis of their past experience, their past data, so that they could strategize their sampling -- more frequent for those things that need it, less frequent for those that don't. I think we're getting back to the idea of a little more flexibility, particularly for the sampling.

DR. HAYES: So go back and review their past history and see what's there. It's always good to do that.

DR. RUZANTE: On section 204, as we saw in the presentation today, there are seven criteria they have pointed out, and I think some of them might be applicable to those. I think that goes to the idea that, as an agency, it would make sense for them to have some sort of uniform -- it still needs to be flexible but try to get, I don't want to say one tool because that could be just too proscriptive, but try to get one approach that could allow you to just look at the most significant contaminants or the products with higher risk, or the food-pathogen combination.

For 104 there are no specific criteria, but for 204 there are, so I think they also should be looking at

those criteria that have been mandated. I don't know if we, as a committee, want to take a look at those and say they look good or they should add more to this.

DR. SHREFFLER: Maybe one other fact for consideration is there's reference to the reporting survey, the RPR or something like that, the adverse events basically. I didn't hear much reference to that in terms of really using it as a means for surveying. Presumably that is done, but it seems like that is one obvious way to be responsive to the public - to evaluate those systematically and track them down when they seem credible and reproducible in numbers.

Again, I'm sure that I'm naïve about the extent to which that is already happening but it's an obvious way to be responsive.

DR. SANTERRE: I very much agree with you. One of the challenges with the adverse events monitoring system is there is no medical follow-up to try and connect the actual medical event to a specific compound or exposure. So that was one of the big limitations. If it was added to it, it would increase the value of that quite a bit.

DR. SHREFFLER: Yes. There are examples of foods that have come to market that are fairly novel in terms of their presence in the food chain -- GMO things or things derived from insects or fungi or whatever where allergy

questions have been raised and probably other questions.

The data are hard to interpret because they're not very high quality, but that would be an easy thing to do better, sort of along the lines of what the CDC does.

DR. HAYES: Anything else on one?

DR. SANTERRE: Could I add one more? The purpose of the data. We've talked a little bit today about is it to regulate the industry to make sure things are being done properly. Is it used to estimate consumer exposure? Or is it to catch high-risk contaminants? You all may add to that list, but I think those are the three that come to my mind. What's the purpose of the data?

DR. HAYES: Okay. Number two: In the development of models to identify and rank priorities, what factors or criteria need to be considered when aggregating or binning foods and chemical contaminants in the food?

DR. SHREFFLER: Mr. Chairman, could I make a suggestion on one aspect of the binning, which we've talked about a few times, sort of the nature of that contaminant and maybe suggest that it be binned a little bit differently. I suggest for discussion maybe infectious organisms; toxic substances, divided into acute and chronic or those with acute and chronic effects; and, three, allergenic.

To the point earlier about samples, I think

samples should and would, in many cases, be appropriately evaluated for the presence of multiple of these depending upon the context. But for purposes of thinking about what the goals are and what the risks are, to this question in the development of models to identify and rank priorities, I think some different binning -- perhaps what I've suggested or perhaps what emerges that's even better from the group would be an improvement.

DR. SANTERRE: Do we handle infectious organisms, or is that outside the purview of this group?

DR. SHREFFLER: I thought the survey we saw reported on Salmonella, Campylobacter, et cetera. That's what I mean by infectious organisms as opposed to food poisoning because of elaborated toxic substances like tularemia or whatever.

DR. SANTERRE: So the question remains I think is that really in our purview or not?

DR. HAYES: They talked a lot about it.

DR. SANTERRE: We talked about antibiotic resistance, and I see that as a little disconnected from where we're going with our questions. I don't know if anybody agrees with that.

I think the health impact for humans eating antibiotics is pretty low. The impact to U.S. agriculture if we lose antibiotics because the organisms are all

resistant could be quite a bit higher. I think it kind of crossed on what this committee might focus on, and it was moving out of our jurisdiction or our assignment.

DR. MEYER: I saw the justification for that discussion was the use of antibiotics in the animal feed so we don't develop microbial resistance.

DR. SANTERRE: Right, but that is not really looking at it as a human health hazard.

DR. MEYER: No, but the focus is on the chemical antibiotic, the chemotherapeutic for the animal.

DR. SANTERRE: Yes, for the animal. But is that in the purview is what I'm asking.

DR. MEYER: I don't know. But that's what I thought was the justification for bringing it here, under chemical.

DR. WILLETT: I interpreted it more broadly, that in their big screen, this whole document, is a whole list of antibiotics that they look for in human food and those are regulated. Is that what you mean?

DR. SANTERRE: Yes. There are tolerances for all those animal drugs, and as an enforcement role for the Agency, they have to make sure that they are below certain concentrations in the animals when they're harvested. It's less human public health and it doesn't really connect to the building of antibiotic resistance, which is an

important problem but I see it as coming outside the jurisdiction of what we're asked to talk about.

DR. WILLETT: I don't think so. Those are two separate problems, but there is drug sensitivity that gets into the allergy area which is a real issue. You're both sensitizing people and precipitating allergic reactions.

DR. MEYER: I agree there is a second class of chemotherapeutics that are in our food that are going to damage or pose a risk to us.

DR. RUZANTE: There is an argument that, for example, in Salmonella there is multi-drug resistance. If your chicken was contaminated with Salmonella, drug resistant, there is evidence that you have higher hospitalization rates for those kinds of pathogens, so they are believed to be slightly more virulent. Then you could say that the burden of illnesses, for example, from Salmonella that are multi-drug resistant versus a Salmonella that is not drug-resistant, they are different because one would require way more hospitalizations and maybe a higher death rate than the one that was not.

I'm just saying that they haven't done that; they have not differentiated between an organism that is drug resistant versus one that's not yet, but it's something that we believe needs to be done. Yes or no.

DR. SANTERRE: I agree with that and everything

you said, but is it in our purview? That becomes a pathogen issue on the Salmonella that's antibiotic-resistant.

DR. RUZANTE: I think it is. We might say this is a type of risk, a hazard, that we want to see addressed, so I think it is. Or we might say no, we think this is not necessarily an issue. You should just go with Salmonella overall and not drill down to whether it's drug resistant or not.

I was a little confused on your question of infectious diseases. I think we are talking about infectious diseases because Salmonella, Campylobacter, E. coli are all infectious diseases.

DR. SANTERRE: Yes. So, is that in our purview? That's the question. Are we dealing with listeria? Are we dealing with Salmonella? I didn't understand that we were. I thought we were dealing with chemical hazards.

PARTICIPANT: No.

DR. SANTERRE: Do we have a microbiologist in this group?

DR. RUZANTE: I wouldn’t say I am a microbiologist. But I am definitely not a toxicologist.

DR. MEYER: I don’t think that is in our purview, the microbiology. But I think the chemical antibiotics that relate to the microbiology are, and then I think

there's a second class of chemotherapeutics which includes those compounds like chloramphenicol, or the beta-adrenergic, some of those.

DR. RUZANTE: Are you talking specifically about this question number two? Or are you talking about in general? In general, I think it is in our purview. But I read question number two being foods and chemical contaminants in food, so I wonder if question number two is just narrowing down to just chemicals.

DR. McBURNEY: To me, this is an important discussion but I think it's also way bigger than we are. The first part and the reason it comes up is because the FDA has a responsibility to make certain that there isn't higher than a certain level of antibiotics in meat products typically where it started that we consume. So there is an enforcement component of monitoring to make certain that that happens.

Whether those sources are high enough -- and I've never heard of them but I'm not an expert -- in terms of whether to cause an allergic reaction, they can be if I take them orally. But whether anybody gets them from a foodborne source I don't know the answer. To me, that's a regulatory, a not approved for use to be present at a certain level in a meat that I buy, so they're monitoring it like they are other chemical entities.

And then there's the second part that skirts around it but is separate in terms of is there a level of Salmonella that shouldn't be present in this food that I'm going to eat. And whether that Salmonella is resistant to an antibiotic or not isn't the issue; it's just whether it's microbially contaminated with Salmonella.

DR. SHREFFLER: And that latter would be outside the purview of what we're speaking to and outside of what the FDA is directly regulating. In other words, just a level of bacteria.

DR. McBURNEY: I am not sure what the regulations are, but that's where they are monitoring in terms of looking, I thought. No? Maybe not.

DR. SHREFFLER: They are monitoring in that way in part; they're counting colonies of both antibiotic-resistant and non-resistant organisms.

DR. HAYES: It seems to me that you've said at least three bins -- chemotherapeutic agents, industrial chemicals broken down into acute and chronic, and allergens.

DR. SHREFFLER: I would suggest toxic substances might be more inclusive than just chemical agents and that could, for example, include the microtoxins.

DR. HAYES: Just chemicals.

DR. SCHREFFLER: As opposed to allergens, though,

because the mechanism is so fundamentally different, and obviously this is my bias but I guess that's also why I'm on the committee.

DR. HAYES: Well, allergens are separated out.

DR. SHREFFLER: I think it's really hard to think about risks related to allergy in the same way. I actually think the risks, in terms of just cross-contamination questions, whether it's antibiotic or unintended allergen exposure, is probably very, very low. But I think it needs to be thought about differently.

DR. ARMBRUST: Wayne, I've got another criterion here, too. One criterion I think that needs to go into this, too, is technology that's used in either manufacturing the food or in the agricultural practices used to grow the food. As that changes over time, that's going to change potential contaminants. This should all factor into different HACCP programs, but that does need to be taken into consideration for model development -- food manufacturing technology and agricultural practices.

DR. LINKOV: I think I have a fundamental issue with this question. What kind of models -- it says in developing models to identify and rank priorities. Depending on the models, it may be different criteria, and even what we mean by criteria may be different in what kind of models. Are we assuming -- it was presented like

different models here. Which models is this question asking about? Is it the last model or the first two models? They are very different. Some of this last model cannot even take this criteria, right? It is irrelevant in a sense.

DR. SHREFFLER: Regardless of what model is adopted, I think the question is still logical in the sense that in the development of models -- put models in quotes for the moment -- what criteria would we think are relevant in the development of those models. It's a valid point; it's vague. But I just think that however you're going to model risk around the chronic toxicity of a chemical additive or contaminant versus however you're going to model the risk related to an allergen or an acutely toxic contaminant, those need to be separated.

DR. LINKOV: But these models, at least the first two that we heard today, integrate across the criteria. Then the question is do you need to really separate this. Is it important? Is it important to know whether it's an allergen or carcinogen? We don't know.

DR. SHREFFLER: But I think we would weight aspects of those models. For example, the variable that many of us talked about -- how do you weight each of those. We might weight them differently depending upon whether something has a very low risk but a very dire consequence

versus something that has a moderate cumulative risk over years.

DR. LINKOV: We may or we may not -- let me give you an example. Say we're talking about nano(?) materials. It's not here, but we have no idea what mechanism of actions we have, but we somehow need to make a decision. So this bends on kind of mode of action doesn't make any sense because we cannot do that, right?

DR. HAYES: Just to follow that up, how much biology do you really need to know to develop models? A good modeler will tell you none, but a biologist will tell you that you need a lot.

DR. SHREFFLER: When will a good modeler, when we know the biology is different, still lump them together? I don't know; I'm the biologist in this discussion I guess, but it seems counter-intuitive to me.

DR. MEYER: Do we want to bin them on mode of action or do we want to bin them on exposure? Classically, it looks like they've been binned on exposure.

DR. HAYES: I think what they are doing is they're binning on exposure. There's no hazard, biology, mode of action that I heard today; it was all exposure.

DR. WALLACE: I thought I heard several speakers today talk about what's driving this whole thing is public health outcomes. It's not exposure, it's not hazard, it's

not cancer, it's not allergy; it's public health impact. So when they develop models to rank priorities, I think it's based on the public health impact. You start at the top, I think is how you classified them. Start at the top and look at outcomes and have the data define the model rather than the other way around.

DR. RUZANTE: Yes. And if you remember, for the most significant contaminants, their ranking was on the causes and the DALYs, so that takes into consideration not just exposure. This is public health impact.

And then, for 204, you have a series of criteria that was also more on exposure.

DR. HAYES: Help me with what you mean by public health impact. Is it what the public thinks the impact is, or is it the real public health impact?

DR. RUZANTE: No. Public health impact means you have a number of illnesses, number of hospitalizations, number of deaths. You also have, for example, for pathogens such as Salmonella, you can have some percentage of cases that might develop reactive arthritis, so you have a percentage of cases that are going to go forward with that.

Then you calculate all that and you say under this percentage of hospitalization, what is the percentage of people who develop long-term (?) or whatever, are dying,

and you do that for each of the pathogens, you arrive at a cost.

DR. HAYES: And then based on that, why are we even concerned about chemicals?

DR. RUZANTE: And the cost is one measure, and Dali is another measure that --

DR. HAYES: How do you measure a hospitalization for aflatoxin?

DR. SANTERRE: It may be broader than that. It may not be deaths, but if you have four trace elements that exceeded what we consider a safety limit and you only had resources, as an agency, to go after and deal with two or three, you might use that priority to say, okay, we're going to use our resources --

DR. HAYES: But is that a public health outcome?

DR. SANTERRE: Yes, if you're exceeding the safety limit. That's the determination. If you've determined that these four are above what we think is safe exposure for consumers, and we know we only have --

DR. HAYES: I still ask you, is that a public health outcome? We think that's what is going to happen, but there's no outcome.

DR. SANTERRE: It's focused on public health in making the decision.

DR. RUZANTE: Do you have any data that could say

under those circumstances there is a likelihood that .001 percent of the population is going to develop this type of cancer? So if you have that for aflatoxin, it doesn't matter if it's 50 or 60 for now; you can. You are going to be able to say, especially for cancer, you have costs for cancer patients so you can say this case is going to cost this. You're also going to say Dali is the type of measure that takes into account disability. So you measure suffering of this person that has cancer for X amount of years until he dies.

DR. HAYES: The only place I can see you can do that is with cigarette smoking from chemical --

DR. RUZANTE: Not really, no. You can calculate Dalis for chemicals. The only thing is I can recognize that you're going to have data gaps, lots of data gaps, but other countries have done it. And you have something from WHO because the global burden of diseases there, they calculated Dalis for several infectious diseases and I believe also cancer.

DR. McBURNEY: I think we are moving into the policy discussion that is beyond our scope in the sense of how they rate them. I read this sentence somewhat differently. In the development of models to identify and rank priorities, what do they do, what do they think about to aggregate and bin them? It's not saying which are the

most important ones, but how should we bin them to do that.

Part of the answer ultimately is policy, but I think that what I heard today was mostly about exposure, so they were either some assessment of this is going to be really bad news and we've got to get ahead of it, and it's based on an exposure model. So there's a risk assessment in terms of is this the most toxic metal that we have. And we have a large number of people.

But I think they're asking how do you aggregate or bin, and I personally think the answer sort of gets solved if they're measuring more and more things in every sample because they they're going to be able to bin across those categories more than they have in the past when they said, you know what, this is seafood and we just measure this in seafood. This is poultry; we measure this in poultry. This is cereal grains; we measure aflatoxin. The broader they are in their mandate, the more tools they have to figure out how to aggregate.

DR. WILLETT: I think that's right. The public health part of it does come in where they're setting priorities, but in terms of practical issues like the binning, then that's a different issue. You do solve it if you analyze everything in every food. They're not going to go to that extreme, but steps have been taken to reduce that.

Then a lot of the binning depends on which potential groups of chemicals or contaminants tend to travel together and are likely to be found in the same class of foods, whether it be fish, dairy products or vegetables.

Another practical consideration is what can you analyze together in the same mass spec run or the same GC run or whatever you use.

DR. McBURNEY: Another idea is it's sort of the canary in the coal mine, and in a sense, if they're able to have multiple analyses more easily on foods, they could actually start to identify signal foods or categories that they can do a more extensive analysis on that then helps them to know where to go in a category.

DR. WALLACE: I was just going to follow real quickly. I agree that we talked most today about exposure so we're looking at a probability of an adverse outcome, but we may also want to bin on hazard. Let's not spend a lot of resource worrying about having a large number of people getting sick to their stomach or nausea or whatever, but let's not ignore that we may have a small number of individuals that will have a very severe adverse outcome. It gets back to low probability-high risk or high probability-low risk.

DR. ROSS: As I think back to this morning, I

think we heard an example of tropical fruit, and there was the mango and some tropical fruit I didn't recognize, so I think what they may be asking us is, for surveillance purposes, is it adequate to screen tropical fruit. And then, maybe for another purpose like, if you found something, you would then want to go back and do them unbinned.

The purpose may depend upon whether you bin or don't bin, whether it's screening, surveillance, or whether it's more analytical. But as I recall, that was an example they gave -- if you look at tropical fruit as a category, as a bin, or you look at each one individually, which increases the workload.

DR. MEYER: With this question, are they implying that maybe they can take all those tropical fruit and throw them in a blender and analyze everything and then screen, and then if you get a hit then you separate it out? Or are they suggesting binning for the purpose of risk assessment where you would put all the tropical fruit in a category and then do your risk assessment? I'm not quite sure what they're getting at.

I keep sensing that they wanted us to answer some issues with efficiency because if you do the whole matrix, you do your 200 by 5 by 100 factorial, it's just impossible to do. I'm not quite sure what they mean by binning.

DR. SANTERRE: I had that challenge with that question, too. If that's the way they interpret it in the total diet study where you're putting your stew, all the components in stew and grinding them up and analyzing them, and then you might go out and say, oh, we got high levels of this; let's go look at the potatoes, let's go look at the meat. But that question confuses me, also.

DR. MEYER: That would be a classic screening technique to narrow down efficiently.

DR. RANGAN: For binning, I just wanted to put methodology consistency. You can't bin things that weren't tested in a similar way, so you need to look at the methodologies before you actually throw things in a bin together.

And I guess my last point is I think we are absolutely here to deal with antibiotic resistance. CVM regulates the use of antibiotics. It's in FDA purview, I think to Juliana's point. The Foster Farms outbreak alone shows that more virulent strains that are more drug resistant have higher levels of hospitalization rates, so we have that data. We have criteria to use, and it's something we should be talking about. It's an acute hazard with an actual empirically demonstrated public health outcome.

I just want to throw in my vote that we must do

that. And we heard from NARMS today. We've heard all sorts of presentations regarding pathogens but also antibiotic resistance, and I think it's critical for us to at least make mention of that. We don't have to solve the problems through microbiology, but I think we need to say that we think they are incredibly important to prioritize.

DR. ARMBRUST: And there is a microbiologist on the committee but he is just not here.

DR. WALLACE: If I may follow on that, I don't disagree with you that there has to be some sort of surveillance for antibiotic resistance. The question is whether it's in the purview of this meeting here whether we address that, and I don't have the answer. But I have a question. In what I see here as surveillance programs, testing programs, compliance programs, we're testing to the level of the tolerance. This committee doesn't necessarily set the tolerances in the various food contaminants; that's done somewhere else.

DR. RANGAN: But are we doing that with pathogens? We're not setting tolerance with those.

DR. WALLACE: Right. But if this committee is looking at a testing program which is designed to test to the tolerance level, then the question is, that antibiotic resistance, is that taken into consideration by whichever committee outside of us is setting that tolerance? We're

just testing to that tolerance already.

DR. RANGAN: I think it is more nuanced than that and I don't think everything has a tolerance. Even chemicals. I think where there is illegality we have zero tolerance. I think with pathogens we have often presence or absence. Ready-to-eat foods aren't supposed to have pathogens, period. So it's not a tolerance; it's an absence or presence.

DR. WALLACE: The question is what is the purview of this committee, or the charge to this committee.

DR. RANGAN: As it relates to public health outcomes in food.

DR. WALLACE: Right, but we are not testing public health outcomes; we're using that as an input into setting risk-ranking priorities.

DR. HAYES: Before we go any further, it is 4:46. Our van is supposed to be here to go back to the hotel about 5:15, so we'll keep going in just a minute.

We passed out to you a meeting evaluation feedback form. FDA would very much appreciate your comments. If you could bring them back tomorrow when we return, give those to Karen at the beginning of the morning.

I think everybody has stepped up and said they would write a nice little paragraph or so about some

various things. If you could have those ready for us, that would be great, too, in the morning.

DR. LINKOV: I still don’t know exactly what they mean by binning, but I'd like to mention that we are now working on a project for the Environmental Protection Agency on exposure-based chemical prioritization, and the way we approach it is we look at two main criteria which include chemical properties and life cycle properties, and on the chemical properties we consider what makes this chemical toxic or driving risk which is persistence by accumulation and toxicity.

On the life cycle properties it's more like how it's used. We have production, consumer use and disposal. So those kinds of metrics or bins are really structuring the way EPA is looking at exposure-based chemical prioritization.

DR. HAYES: Any other thoughts or comments? Let's spend a little bit of time on the third one. When using a risk-scoring process, what factors or criteria should be considered in deciding where to draw the line to identify scores that are higher versus lower risk?

DR. LINKOV: I can start on this one. This is fundamentally the wrong way to frame the question. In this scoring list you're not talking about risk; you're just talking about comparative positioning of these chemicals in

the list of priorities. It's not like drawing the line like we can accept under minus-6 cancer risk; it's fundamentally impossible to do given the methodology that we used here. This number means nothing; it only makes sense in a comparative way.

I guess it goes back to what we discussed earlier. The issue is not so much how we make this list but rather how we use it for decisions, and that should go back to missions and framing of the problem.

Moreover, another important issue I'd like to mention is that the current model that was presented is not really optimal to address the question that they asked in the sense of what they're doing. It's like prioritizing stocks in the financial market by their performance, but this is not how we invest; we build mutual funds that include a combination of these.

Similarly here, the top few may be really correlated and it doesn't mean that all the top five need to be addressed. For example, (?) radionuclides and they are all correlated. It doesn't make sense to have all of them as a high priority. We need to really supplement these models as a next step, this kind of portfolio idea that it's not so much about where to draw the line but what would be the optimal portfolio of chemicals to sample and address, and that's probably the next phase of these types

of models. So that's my take on it.

DR. WALLACE: I don’t know if this is a fair question that they're asking us because they're basically saying let's take the 2,000 industrial chemicals, the 600 pesticides, the 31 microtoxins, and let's put them into three baskets. And Congress is going to give us enough money to work on everything that's in the high basket. That's not how it works.

I think what we're really asked is a continuum. When they ask us to prioritize, it's a continuum. You spent the first $100.00 on that chemical food pair that is at the very highest. Then your next $100.00 you spend on the next one and you work your way down.

To categorize them into high, low and medium I think mis-represents what the whole process is.

DR. WILLETT: I think that is true, but I think they're really asking us what criteria do we use to establish priorities, realizing that they have to draw a line someplace given budgetary constraints.

DR. WALLACE: They have already told us the way that they're going to do it, and that is a public health outcome-based, science-driven risk prioritization. And I agree with that.

DR. WILLETT: Okay. That is probably what we should say.

DR. MEYER: The reason I want us to say something is they can then go and justify that it's science based because the experts have put the imprimatur on it.

DR. WALLACE: But if we don’t draw those lines and just leave it as a continuum, it's still scientifically based.

DR. HAYES: Dr. Wallace, if I remember correctly, you do not have a paragraph, and you just got your paragraph.

DR. SANTERRE: One of the challenges is that what FDA has talked about today is things that have tolerances. EPA set 600 tolerances and most everything that's being looked at has a tolerance. What about those things that have no tolerance? Most of those industrial chemicals don't have any safety limit, so the problem is what do you do when you find them there. It seems like we're a little scared to look for them because we don't know what to do. They didn't tell us today what their course of action would be if they started to detect some of these in their screening. That's a challenge that I think the Agency has to look at down the road.

DR. WILLETT: That is an interesting question. One of the factors that we'll presumably be influential in deciding what is a priority to look at would be -- there's a ton of it in the food supply. That is one consideration,

that one of these chemicals without a tolerance level, if it's found in large amounts in the food supply, it would be useful to try to learn more about what that meant.

DR. SANTERRE: And FDA has kind of taken that approach. I don't know to what degree but they're going down this road of the TTC, the Threshold of Toxicological Concern, which suggests that in a Delaney paradigm, every chemical is toxic at a certain concentration, but also, every chemical is safe at a certain concentration. So they're trying to define the line of concentration at which all chemicals would be safe, with a few exceptions. If they test down to that level, looking not just at concentration in the food but at human exposure, things we eat a lot of like potatoes, the concentration would be a lot lower allowed. But basically using the concept that anything that goes above this increases the risk and our concern about that chemical. They didn't talk about that today but they are exploring that.

DR. SHREFFLER: The hazard-ratio concept might be another applicable place, perhaps.

DR. HAYES: Are you ready to quit for today? Let’s do it. Thank you for an excellent first day. We'll wrap it up tomorrow.

(Whereupon, the meeting adjourned at 4:55 pm)